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Enantioselective Iridium-Catalyzed Carbon–Carbon and Carbon–Nitrogen Bond Formations

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Enantioselective Iridium-Catalyzed Carbon–Carbon and Carbon–Nitrogen Bond Formations

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August 2020

Dedication

To my family

and

Thomas

Acknowledgements

First and foremost, I would like to thank my parents – Jay, Patricia, and Michael – for their never-ending love, support, and encouragement. They have always supported me in every challenge I have undertaken and were there for me through all the highs and lows I have encountered during my academic career.

I would like to thank my advisor Michael Krische for his support and the numerous opportunities he has given me throughout my graduate career. His infectious passion for chemistry and drive to help his students be the best versions of themselves have made me the scientist I am today.

I would also like to thank Craig Stivala and Jason Zbieg for their guidance, advice, and the opportunity to explore an industrial career during my summer at Genentech.

The staff in the Chemistry Department are phenomenal. Thank you to Betsy Hamblen for help navigating the graduate program. Thank you to Steve Sorey, Ian Riddington, and Vincent Lynch for their help with NMR studies, mass spec studies, and X-Ray crystal elucidation. I would also like to extend my thanks to the Graduate School for awarding me a Provost Graduate Excellence Fellowship, providing funding for my research and conference travel throughout my tenure at UT Austin.

I am beyond grateful for all my fellow lab members and for the friendships that have extended beyond the workbench. To Michael Holmes, thank you for your guidance and patience, teaching me the basics and helping me find my footing to be independent. I am grateful for the opportunities I had to collaborate on various projects with Tom Luong, Khoa Nguyen, Gilmar Brito, Seung Wook Kim, Kim Spielmann, Rob Swyka, and Ming Xiang. Many thanks to my fellow graduate students for their support and friendship:

Rosalie Doerksen, Nancy Huynh, Woo-Ok Jung, Brad Hu, Yuk Ming Siu, Binit Sharma Poudel, and James Cabrera, just to name a few. A special thank you to my roommate and fellow chemist Caroline Hinson, who is always there with a delicious baked good and an open ear.

Finally, I would like to thank Thomas Hüfner for his support throughout this journey. Without his love and encouragement, I would not be the person I am today. Thank you for being my rock, confidant, and best friend.

Abstract

Enantioselective Iridium-Catalyzed Carbon–Carbon and Carbon–Nitrogen Bond Formations

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The University of Texas at Austin, 2020

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Formation of new C–C bonds is a mainstay of modern molecule construction, however methods for the asymmetric construction of these scaffolds has been limited by the use of premetalated reagents or the use of catalytic methods that still require the use of stoichiometric metallic reductants. The Krische group's approach to this bond formation utilizes the concepts of transfer hydrogen and carbonyl addition to form C–C bonds. These processes proceed through the *in situ* formation of a transient allylmetal species which then undergoes carbonyl addition. The research presented herein describes the development of several methods for the enantioselective construction of new C–C bonds, utilizing allenes to form nucleophilic allylmetal complexes that react with carbonyl electrophiles. Additionally, a method for the enantioselective construction of new C–N bonds is described, utilizing branched allylic acetates to form allylmetal complexes that react in an electrophilic manner with non-redox active primary and secondary amine nucleophiles.

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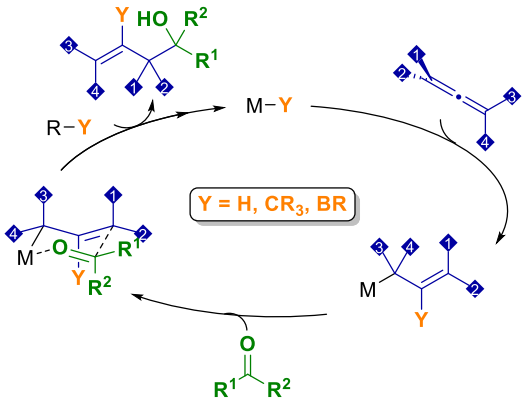
1.1 Introduction

Carbonyl addition reactions traditionally rely on preformed carbanion equivalents from Grignard and related organometallic reagents. These reagents, however, pose issues of safety and usability as many are moisture sensitive or require multi-step preparation and cryogenic conditions.[1] In contrast, *in situ* formation of a nucleophilic allylmetal species from hydro-, carbo-, or borometalation of an allene, followed by combination with a carbonyl electrophile to form products of carbonyl addition, can circumvent these concerns.[2-4]

The general mechanism for these transformations involves formation of a M–H, M–CR_3, or M–BR species followed by respective hydro-, carbo-, or borometalation of the allene to yield an allylmetal species (Scheme 1.1). Typically, this metalation occurs on the least hindered face of the allene; however, ligand effects and substrate-metal interactions can occasionally favor a more hindered addition. These allylmetal species can then either

Scheme 1.1 Generalized Mechanism for Allene–Carbonyl Couplings via Hydro-, Carbo-, or Borometalation



react from their kinetic haptomers, or isomerize by way of σ–π–σ interconversion to more thermodynamically favored haptomers before undergoing carbonyl addition, commonly through a six-centered Zimmerman–Traxler-type[5] transition structure. The product is then released and the M–H, M–CR_3, or M–BR species regenerated.

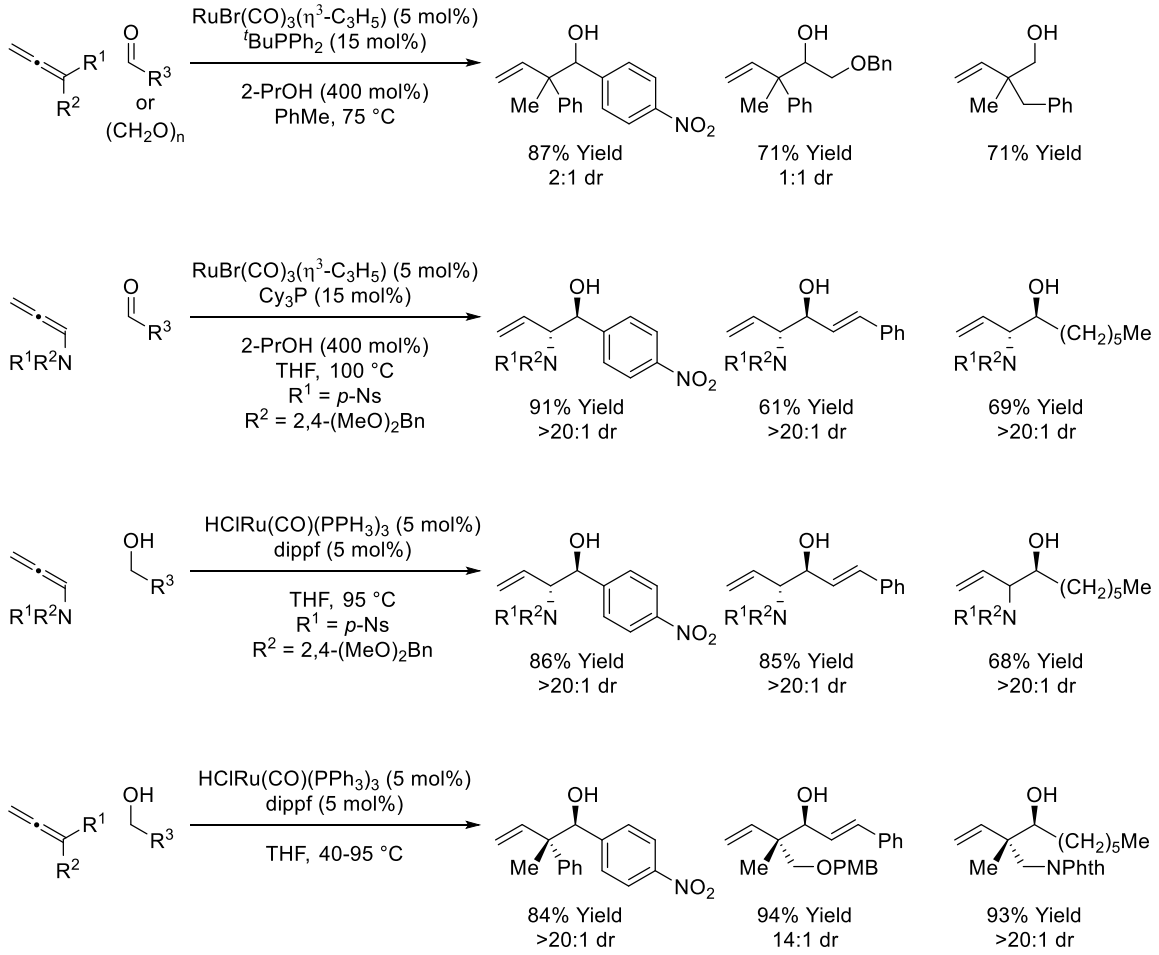
In this review, transition metal-catalyzed carbonyl additions utilizing allenes as pronucleophiles are discussed. Discussion is restricted to processes in which the catalytic mechanism proceeds via a hydro-, carbo-, or borometalation step to produce the reactive allylmetal intermediate. Transformations are catalogued by metalation process and then by metal catalyst. Metal-catalyzed couplings to carbon dioxide are not covered.

1.2 HYDROMETALATIVE PROCESSES

1.2.1 Ruthenium

In 2008, Krische and co-workers[6] identified ruthenium(II) complexes modified by a monodentate phosphine ligand catalyze the reductive coupling of 1,1-disubstituted allenes with paraformaldehyde and higher aldehydes (Scheme 1.2). Utilizing 2-propanol as the terminal reductant, homoallylic alcohol products could be isolated in good yields. Under similar reaction conditions the *anti*-aminoallylation of aldehydes can be achieved utilizing sulfonamido-allene as pronucleophile (Scheme 1.2).[7] The catalytic mechanism of these transformations involves allene hydrometalation to form a nucleophilic allylruthenium species followed by aldehyde addition by way of a 6-centered transition structure. The resulting ruthenium alkoxide then undergoes alkoxide exchange with 2-propanol, releasing the coupling product and forming ruthenium isopropoxide. Following β-hydride elimination, acetone is released regenerating the metal-hydride. In this way, it is possible to exploit primary alcohols to serve dually as reductant and aldehyde proelectrophile.

Scheme 1.2 Ruthenium(II)-Catalyzed Allene–Aldehyde Reductive Couplings Mediated by 2-Propanol or Hydrogen Autotransfer

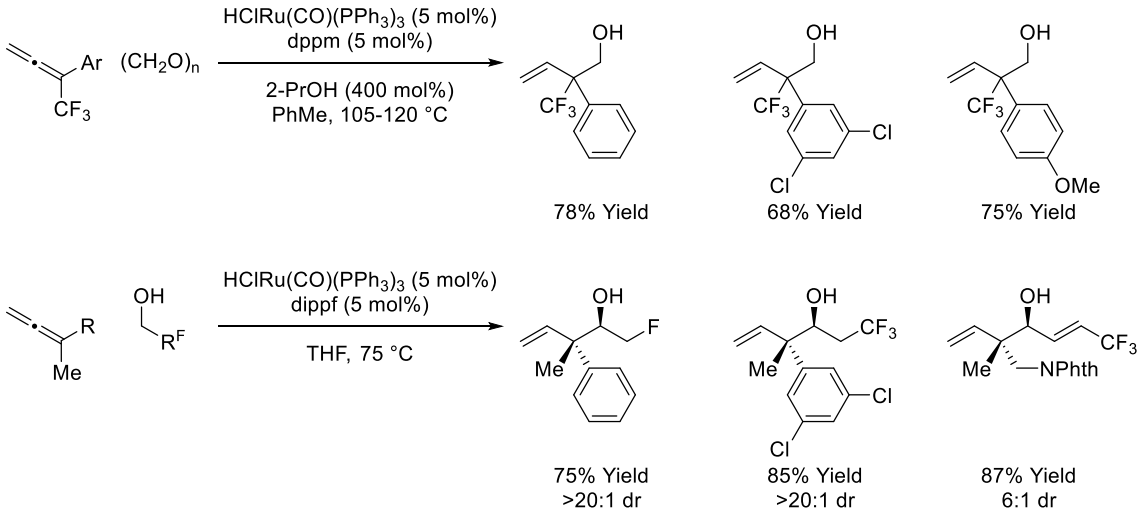


Utilizing the precatalyst $HClRu(CO)(PPh_3)_3$ and the bidentate ligand 1,1'-bis(diisopropylphosphino)ferrocene (dippf) the highly *anti*-diastereoselective formation of vicinal *anti*-amino alcohols can be achieved using primary alcohols (Scheme 1.2).[8] When this catalytic system is applied to the coupling of 1,1-disubsittued allenes and primary alcohols high levels of *anti*-diastereoselectivity can now be observed (Scheme 1.2).[9] The high diastereoselectivity observed in these cases is attributed to a Curtin–Hammett scenario being operative; the (*E*)- allylruthenium isomer provides a lower energy carbonyl addition pathway, which leads to exclusive formation of the *anti*-diastereomer. The (*Z*)- and (*E*)-

allylruthenium species rapidly interconvert at low concentrations, allowing the favored (*E*)-isomer to be replenished.

Krische and co-workers[10] also disclosed that ruthenium(II)-hydride complexes modified by the phosphine ligand bis(diphenylphosphino)methane (dppm) are effective catalysts for the 2-propanol-mediated reductive coupling of CF_3-bearing allenes with paraformaldehyde to form CF_3-bearing neopentyl alcohols in good yields (Scheme 1.3). While 2-propanol is the primary terminal reductant in this system, small quantities of formate esters were identified as minor reaction products, suggesting that paraformaldehyde is also acting as terminal reductant to some extent. Utilizing similar reaction conditions, fluorinated alcohols undergo reductive coupling with 1,1-disubstitued allenes to deliver homoallylic alcohols with moderate to high levels of *anti*-diastereoselectivity (Scheme 1.3).[11] This transformation is significant as many of the corresponding fluorinated aldehydes are not stable or commercially available.

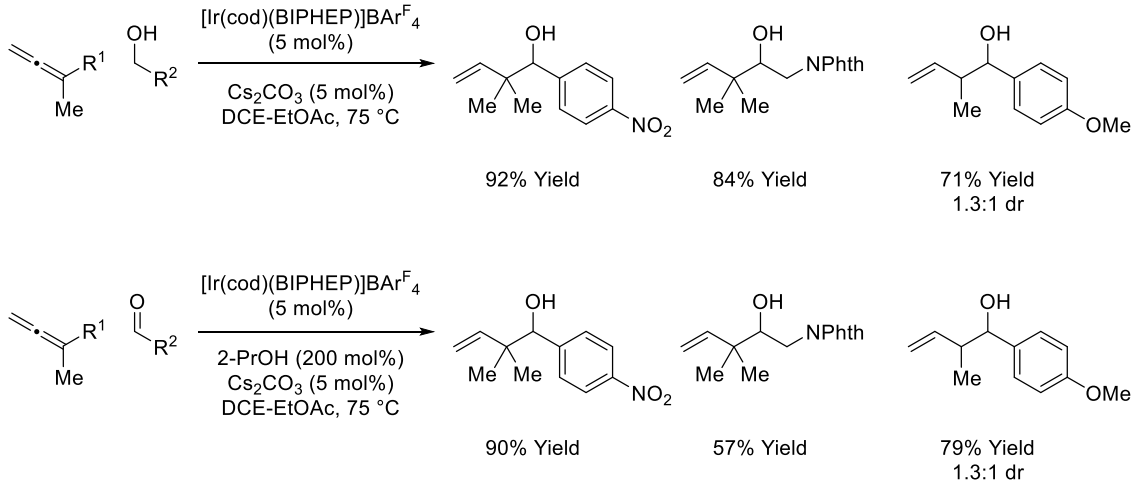
Scheme 1.3 Ruthenium(II)-Catalyzed Allene–Aldehyde Reductive Couplings with CF_3-Bearing Allenes or Fluorinated Alcohols



1.2.2 Iridium

Following their report of the first iridium-catalyzed allene–aldehyde reductive coupling under hydrogenation conditions utilizing hydrogen gas (not shown),[12] Krische and co-workers reported related iridium-catalyzed allene–aldehyde reductive couplings mediated by 2-propanol and hydrogen autotransfer (Scheme 1.4).[13] Using dimethylallene as pronucleophile and a variety of primary alcohols, products of reverse prenylation could be obtained in good yields. Under related transfer hydrogenation conditions, with 2-propanol as terminal reductant, these same transformations give comparable yields. Methylallene and gaseous allene (not shown) could also be utilized, yielding products of carbonyl crotylation and allylation in moderate to good yields.

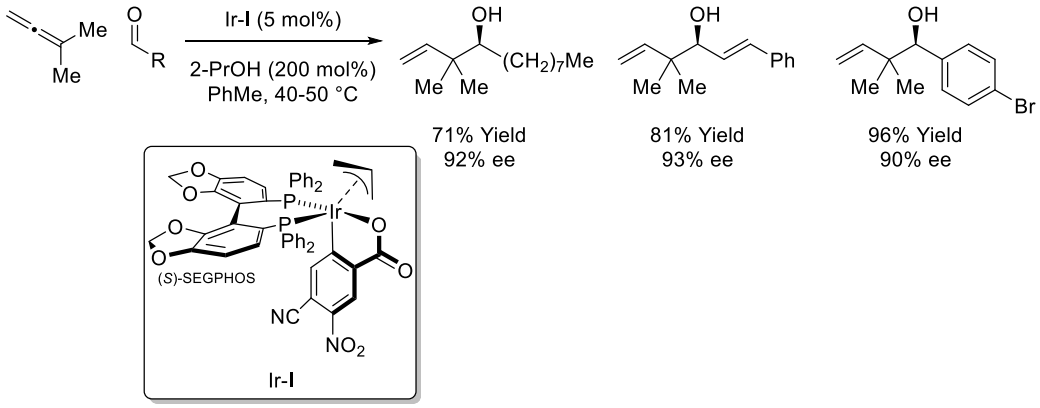
Scheme 1.4 Iridium-Catalyzed Reverse Prenylation, Crotylation, and Allylation via Hydrogen Autotransfer and Transfer Hydrogenation



In 2009, Krische and coworkers[14, 15] reported an iridium(III)-catalyzed allene–aldehyde reductive coupling mediated by 2-propanol (Scheme 1.5). Utilizing a cyclometalated π-allyliridium *C,O*-benzoate complex modified by (*S*)-SEGPHOS, Ir-**I**, aliphatic, α,β-unsaturated, and aromatic aldehydes could be coupled with dimethylallene to produce products of carbonyl *tert*-prenylation in good to excellent yields with high levels

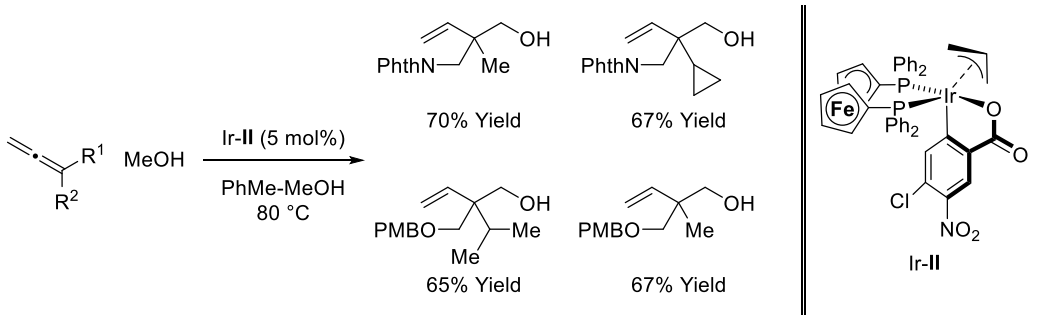
of enantioselectivity. These same transformations could be carried out from the alcohol oxidation level, where the reactant alcohol acts dually as the carbonyl proelectrophile and the terminal reductant (Scheme 1.5).

Scheme 1.5 Enantioselective Iridium(III)-Catalyzed Carbonyl *tert*-Prenylation from the Aldehyde or Alcohol Oxidation Level



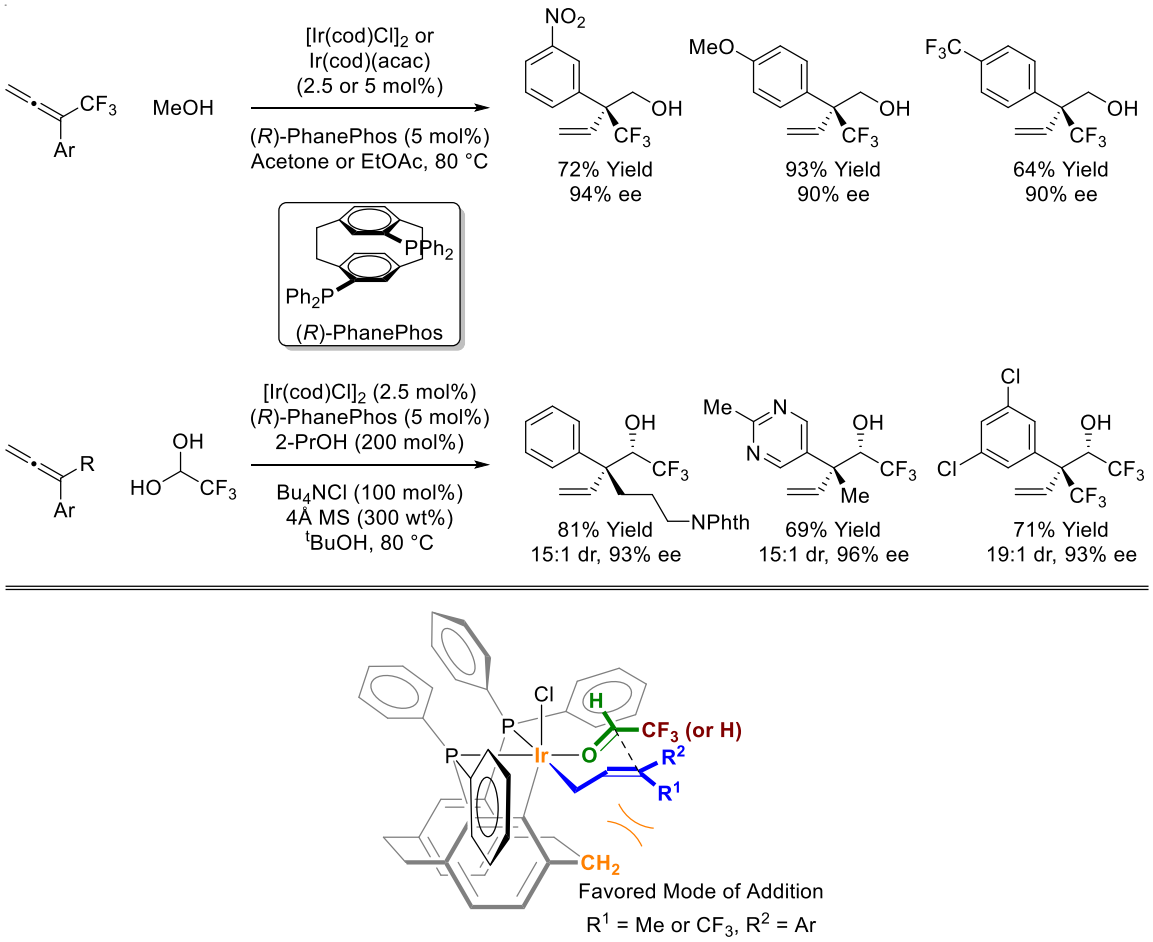
A related cyclometalated π-allyliridium *C,O*-benzoate complex modified by 1,1′-bis(diphenylphosphino)ferrocene (dppf), Ir-**II**, catalyzes the allene–formaldehyde reductive coupling via methanol-mediated hydrogen autotransfer to form acyclic quaternary carbon centers (Scheme 1.6).[16] A variety of 1,1-disubtituted allenes were used to form products of hydrohydroxymethylation in good yields. Kinetic studies identified methanol dehydrogenation, not the carbonyl addition step, to be turnover-limiting.

Scheme 1.6 Iridium(III)-Catalyzed Reductive Coupling of 1,1-Disubstituted Allenes with Methanol



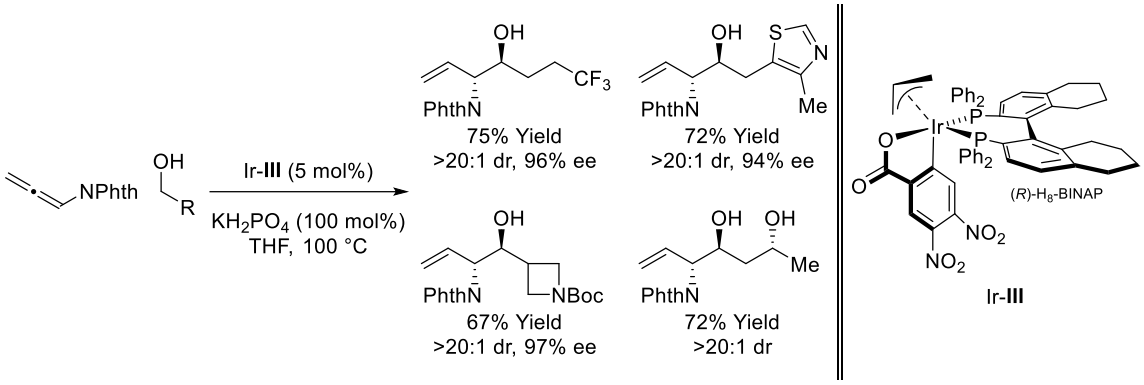
Attempts from Krische and co-workers to develop an enantioselective reductive coupling of allenes with methanol utilizing cyclometalated π-allyliridium *C,O*-benzoate catalysts failed to provide high levels of selectivity. However, utilizing an iridium catalyst modified by (*R*)-PhanePhos, CF_3-allenes react with methanol to form neopentyl alcohols with CF_3-bearing quaternary carbon stereocenters in good yields with high levels of regio- and enantioselectivity (Scheme 1.7).[17] This iridium–PhanePhos catalyst system was further exploited in a highly regio-, *anti*-diastereo-, and enantioselective 2-propanol-mediated allene–fluoral reductive coupling to form CF_3-substituted secondary alcohols that incorporate quaternary carbon-containing stereodiads (Scheme 1.7).[18] Studies examining the effectiveness of the iridium–PhanePhos catalyst in these and related transformations[19] led to the identification of a chromatographically stable cyclometalated iridium(III) complex (Scheme 1.7), in which a four-member metallacycle is formed from oxidative addition to the ligand's paraphane backbone. Crystallographic elucidation of this structure, along with DFT calculations, suggest the observed excellent control of selectivity stems from minimization of steric interactions with the paraphane ligand; the most favored transition state for all of the transformations is that in which the substituted σ-allyl and the CH_2 moiety of the ligand are not in the same plane.[18]

Scheme 1.7 Iridium–PhanePhos-catalyzed Reductive Couplings to Form Quaternary Carbon Stereocenters



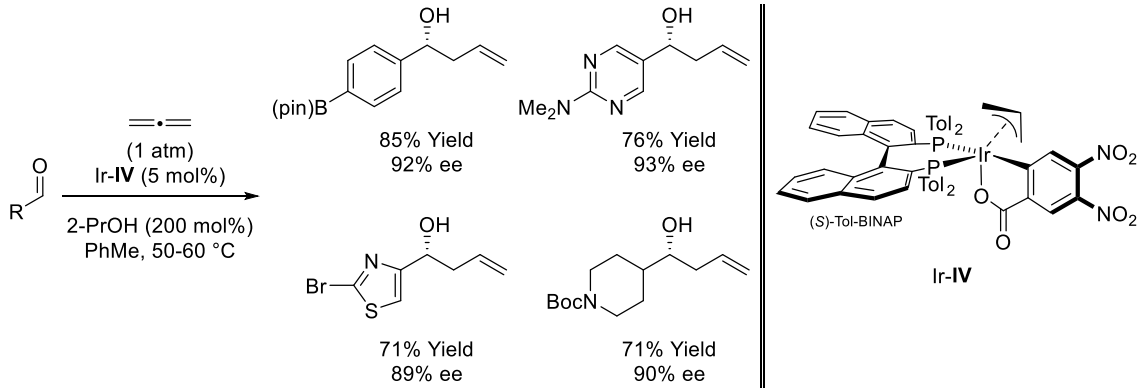
In 2019, Krische and co-workers[20] further expanded upon the utility of the cyclometalated π-allyliridium *C,O*-benzoate catalysts, reporting the first catalytic enantioselective carbonyl (α-amino)allylations (Scheme 1.8). The cyclometalated π-allyliridium *C,O*-benzoate catalyst modified by (*R*)-H_8-BINAP, Ir-**III**, effectively catalyzes the reductive coupling of phthalimido-allene and primary alcohols to yield 1,2-amino alcohols with high levels of regio-, *anti*-diastereo, and enantioselectivity. The use of alcohol coupling partners, which are typically commercially available, is significant as some corresponding aliphatic aldehydes can be relatively unstable and difficult to handle.

Scheme 1.8 Enantioselective Iridium(III)-Catalyzed Carbonyl (α-Amino)Allylation



In an extension of their work in the area of allylation reactions, Krische and co-workers[21] reported the first enantioselective iridium(III)-catalyzed aldehyde allylation mediated by gaseous allene (Scheme 1.9). Utilizing the cyclometalated π-allyliridium *C,O*-benzoate catalyst modified by (*S*)-Tol-BINAP, Ir-**IV**, and feedstock chemicals allene gas and 2-propanol, homoallylic alcohols were formed in good to excellent yields with high levels of enantioselectivity. The authors note an inversion of enantioselectivity was observed in these transformations in comparison to those conducted under identical conditions using allyl acetate as pronucleophile. Experimental and computational studies support this deviation stems from a difference in catalytic mechanism. Allyl acetate

Scheme 1.9 Enantioselective Iridium(III)-Catalyzed Aldehyde Allylation with Allene Gas

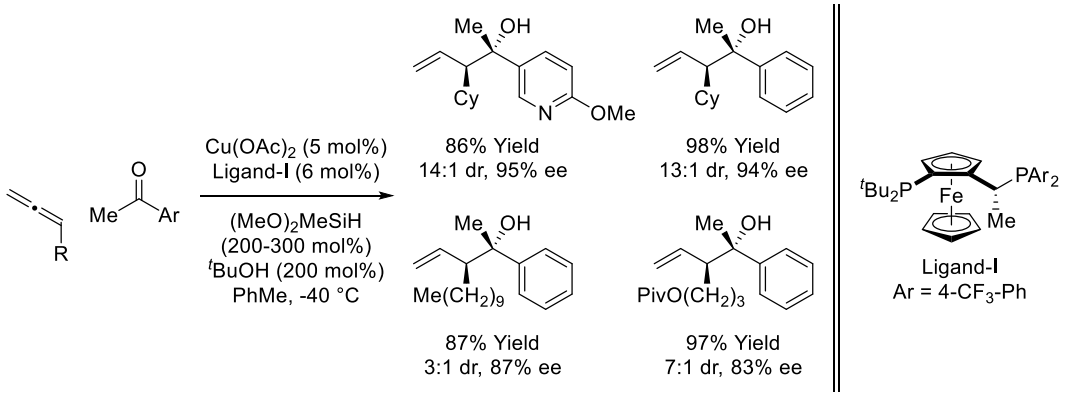


ionization occurs from a square planar iridium species while allene hydrometalation occurs from a pentacoordinate iridium hydride, resulting in the formation of diastereomeric iridium complexes and consequently lead to enantiomeric products.

1.2.3 Copper

In 2018, Buchwald and co-workers[22] reported an enantioselective copper(I)-catalyzed allene–ketone reductive coupling mediated by silane (Scheme 1.10). Utilizing a copper complex modified by JOSIPHOS-type ligand-**I** and a variety of methyl ketones homoallylic alcohols were synthesized with moderate to good levels of *anti*-diastereo- and enantioselectivity. The catalytic mechanism is hypothesized to involve formation of a nucleophilic allylcopper-(I) species from hydrometalation of the allene, followed by ketone addition to give a copper(I) alkoxide. Silane-mediated σ-bond metathesis produces the homoallylic silyl ether, which is hydrolyzed upon isolation, and regenerates the copper-(I) hydride.

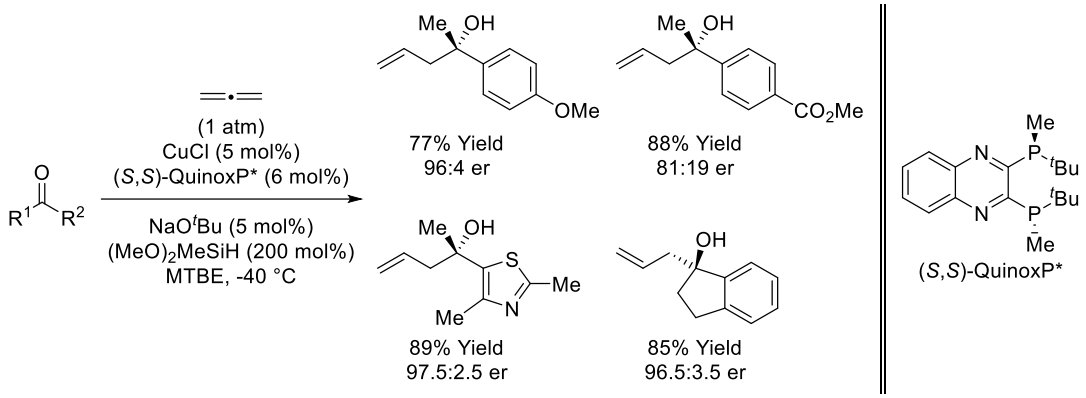
Scheme 1.10 Copper-Catalyzed Allene-Ketone Reductive Coupling Mediated by Silane.



In 2019, Buchwald and co-workers[23] expanded their previous technology utilizing allene gas in an enantioselective copper-catalyzed ketone allylation mediated by silane (Scheme 1.11). Utilizing a copper catalyst and the chiral ligand (*S*,*S*)-QuinoxP*, a wide

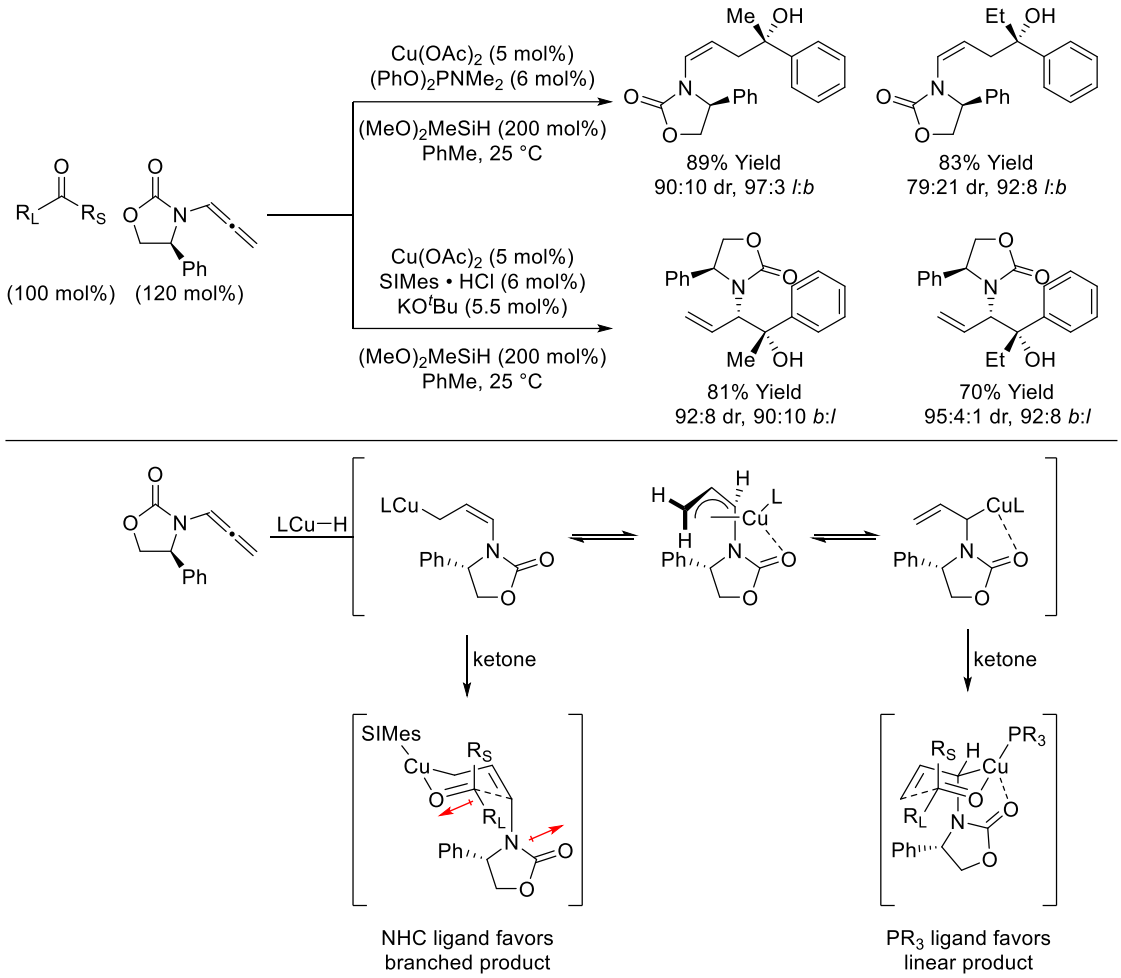
variety of ketones undergo allylation with moderate to high levels of enantioselectivity. *Racemic*-BINAP can also be used to efficiently form the racemic allylation products with high yields. Additionally, under these conditions, more common industrially produced hydrocarbon mixtures of allene, methylacetylene, and propylene can be utilized as the source of allene gas with comparable yields to pure allene gas (not shown).

Scheme 1.11 Copper-Catalyzed Allene Gas–Ketone Reductive Coupling Mediated by Silane



In 2019, Sieber and co-workers reported the stereoselective copper(I)-catalyzed reductive couplings of ketones and a chiral allenamide mediated by silane for the formation of both linear[24] and branched[25] aminoallylation products (Scheme 1.12). Using a copper catalyst modified by either a phosphoramidite or NHC ligand, high levels of respective linear or branched selectivity and moderate to good levels of *anti*-diastereoselectivity could be achieved for a wide array of ketones. However, some loss of selectivity can be observed as the steric bias between R_L and R_S of the ketone is reduced. As with previous examples, the catalytic mechanism is postulated to involve hydrocupration of the allenamide to form a nucleophilic σ-allylcopper species, which can isomerize prior to ketone addition yielding the copper alkoxide. The authors suggest the origin of the observed regioselectivity lies in competition between the strength of coordination of the oxazolidinone ring to copper

Scheme 1.12 Copper-Catalyzed Stereoselective Ketone–Allenamide Reductive Coupling Mediated by Silane.



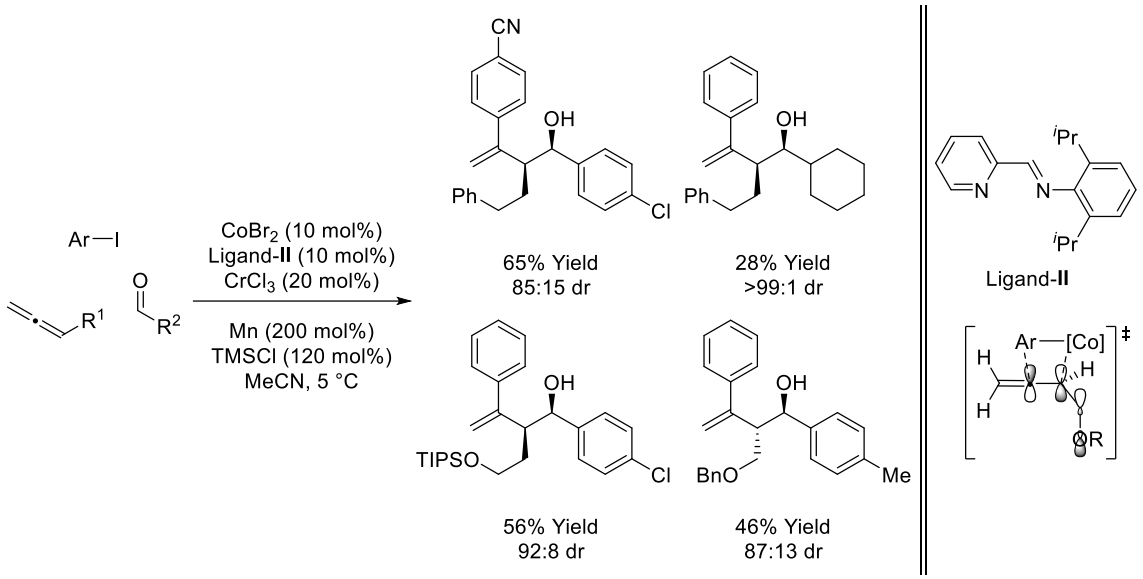
versus the magnitude of $A^{1,3}$-strain present in the initially formed σ-allylcopper species (Scheme 1.12). The poor electron-donating ability of the phosphoramidite ligand contributes to higher $A^{1,3}$-strain in the linear allyl-copper species, as well as increases electrophilicity of the copper center, leading to a preference for the branched allylcopper species. Likewise, the bulky, strongly electron-donating NHC ligand disfavors coordination of the oxazolidinone. Furthermore, dipole-minimization can occur in this chair-like transition structure, leading to formation of the branched product (Scheme 1.12, bottom).

1.2 CARBOMETALATIVE PROCESSES

1.2.1 Cobalt

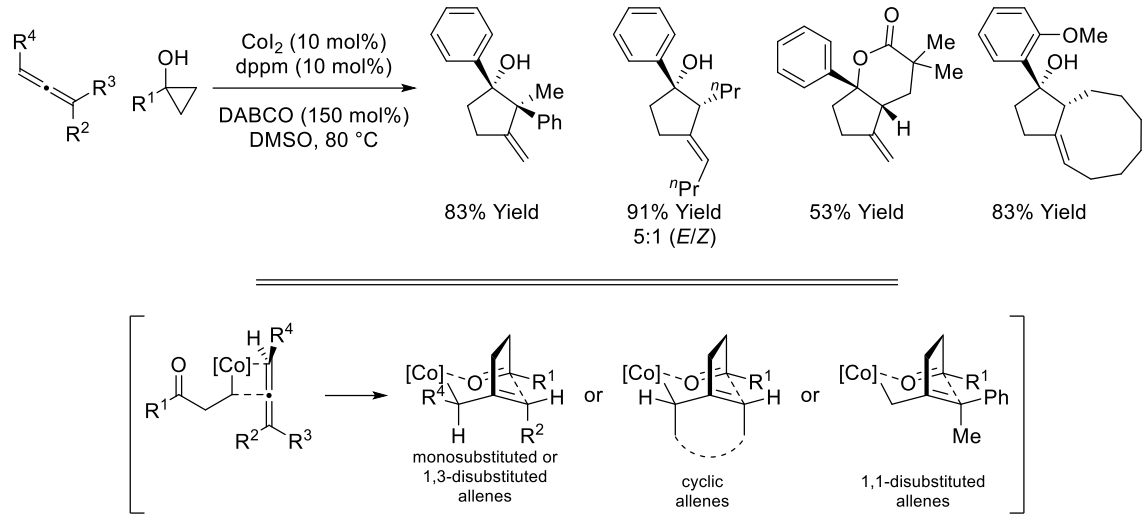
In 2018, Komeyama and co-workers[26] reported a diastereoselective cobalt/chromium-catalyzed three-component aryl iodide–allene–aldehyde coupling mediated by manganese and TMSCl (Scheme 1.13). Homoallylic alcohols could be formed with moderate to good levels of *syn*-diastereoselectivity from a variety of substituted aryl iodides, aryl and alkyl aldehydes, and alkyl monosubstituted allenes. The authors posulate a catalytic mechanism wherein oxidative addition of aryl iodide to a low-valent cobalt species preceeds carbometalation of the allene to yield an aryl-substituted allylcobalt species. A rapid transmetalation event then transfers the allyl moiety from cobalt to chromium with retention of alkene geometry. Carbonyl addition then occurs by way of a 6-centered transition structure to give a chromium alkoxide which is cleaved by TMSCl to give the homoallylic silyl ether, which is cleaved upon workup. Notably, utilizing allenes with oxygen substituents at the allenyl position resulted in products with moderate to good levels of *anti*-diastereoselectivity. The origin of the observed inversion of diastereoselectivity when utilizing these allenyl ethers is believed to result from carbometalation occurring at the more substituted alkene due to hyperconjugative stabilization of the newly forming Co–C bond by the σ* orbital of the adjacent C–O bond (Scheme 1.13, right). The resulting branched cobalt species then isomerizes to the more thermodynamically stable (*E*)-allylcobalt species before stereoretentive transmetalation to chromium. This occurs in contrast to carbometalation of the unactivated allene terminus, which yields the kinetic (*Z*)-allylcobalt species and undergoes rapid transmetalation before isomerization can occur.

Scheme 1.13 Cobalt/Chromium-Catalyzed Aryl Iodide–Allene–Aldehyde Coupling Mediated by Manganese



In 2019, Yang, Yoshikai, and co-workers[27] described a cobalt-catalyzed cyclopropanol–allene coupling giving products of formal (3+2) cycloaddition with high levels of regio- and diastereoselectivity (Scheme 1.14). A variety of aryl and alkyl substituted cyclopropanols react with allenes to form monocyclic and fused polycyclic 3-alkylidenecyclopentanols in moderate to good yields as single diastereomers. The catalytic mechanism involves base-assisted cyclopropanol ring opening to yield a cobalt homoenolate, followed by carbometalation of the allene to give an allylcobalt species. Intramolecular carbonyl addition then proceeds by way of a 6-centered transition structure in which steric interactions are minimized (Scheme 1.14, bottom).

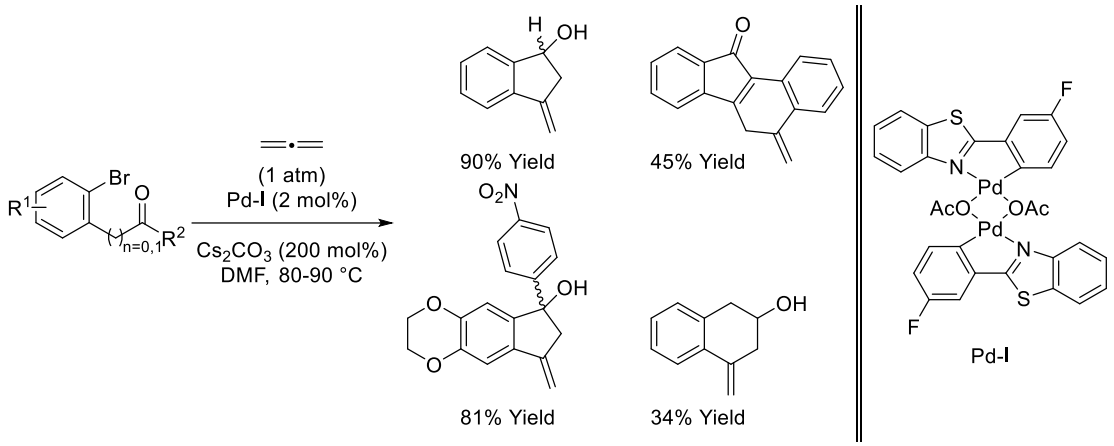
Scheme 1.14 Cobalt-Catalyzed Formal (3+2) Cycloaddition of Cyclopropanol and Allene



1.2.2 Palladium

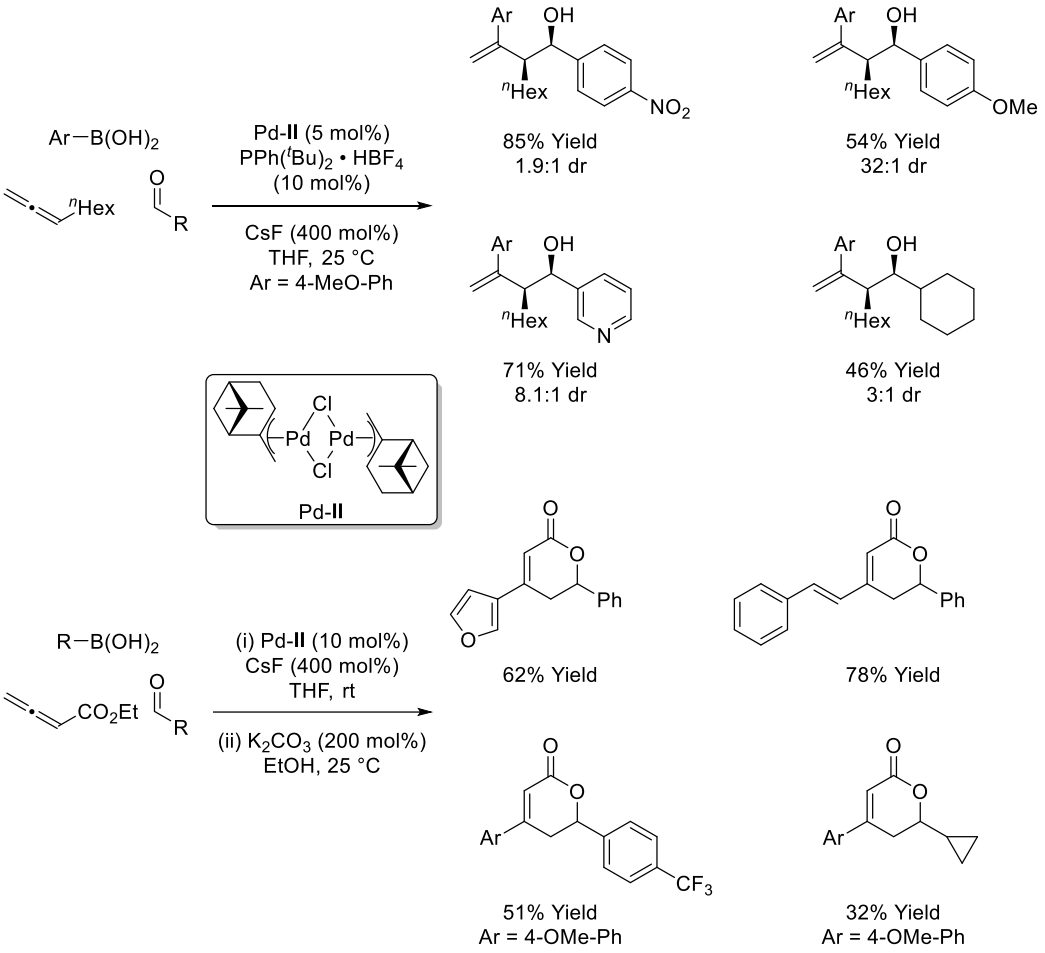
In 2000, Grigg and co-workers[28] reported the palladium-catalyzed coupling of aryl aldehydes and ketones with allene gas (Scheme 1.15). Utilizing a non-phosphine palladium precatalyst, methylene-bearing cyclopentanols and cyclohexanols are formed in moderate to good yields. The authors suggest the precatalyst serves as a source of Pd(0) nanoparticle, which can then undergo oxidative addition with the carbonyl-containing aryl halide. Carbometalation to allene gas under base-mediated conditions with Cs_2CO_3 then results in the formation of an anionic allylpalladium species, which can combine with the carbonyl. While the terminal reductant in this system is not immediately apparent, the authors emphasize the necessity of dimethylformamide as solvent, suggesting formate impurities and decomposition products could be involved.

Scheme 1.15 Palladium-Catalyzed Nucleophilic Cyclization of 2-Haloaryl Aldehydes and Ketones with Allene Gas



The β-pinene-derived π-allylpalladium(II) precatalyst, Pd-**II**, was reported by Malinakova and co-workers[29] to catalyze a three-component arylboronic acid–allene–aldehyde coupling (Scheme 1.16). 4-Methoxyphenyl boronic acid and 1,2-nonadiene reacted with a variety of aromatic, heteroaromatic, and alkyl aldehydes to give branched racemic homoallylic alcohols with varying levels of *syn*-diastereoselectivity. The catalytic mechanism is believed to proceed via a bis-π-allylpalladium(II) intermediate. The authors utilized this methodology as the initial step in a simple 3-step protocol for the diastereoselective synthesis of substituted tetrahydrofurans (not shown).[30] A related coupling was also reported in which an ethyl allenoate, boronic acids, and aldehydes are coupled to form substituted α,β-unsaturated δ-hydroxy esters which cyclize to the corresponding δ-lactones in moderate to good yields.[31] Again, carbopalladation results in a bis-π-allylpalladium species however the authors suggest isomerization to the metal-enolate occurs and carbonyl addition then proceeds via an open transition state.

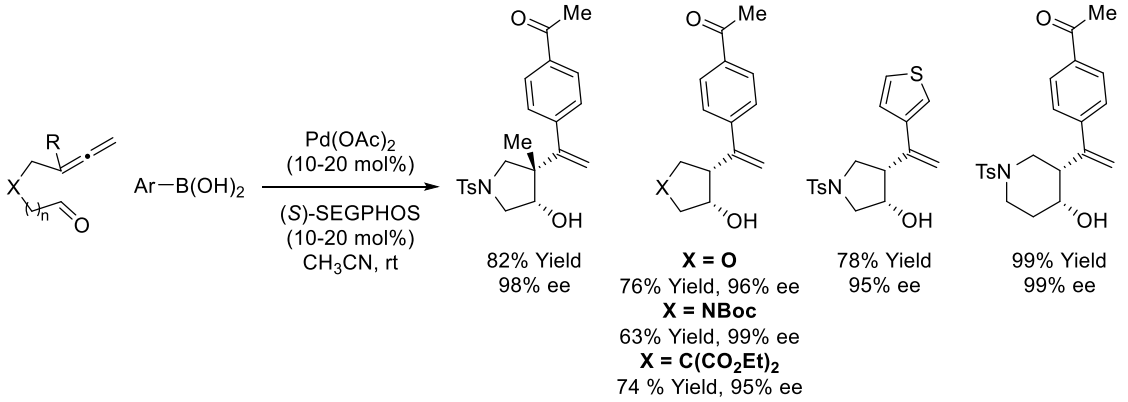
Scheme 1.16 Allylpalladium(II)-Catalyzed Boronic Acid–Allene–Aldehyde Couplings



In 2008, Tsukamoto and co-workers[32] reported the first enantioselective palladium(II)-catalyzed arylative cyclization of allenyl aldehydes with aryl boronic acids (Scheme 1.17). Utilizing (*S*)-SEGPHOS and a variety of allenyl aldehydes with varying tether-lengths and heteroatom substitutions, cyclic homoallylic alcohol products are formed in good to excellent yields as single *syn*-diastereomers with high levels of enantioselectivity. Carbometalation of the allenyl aldehyde by the arylpalladium species, formed from transmetalation of the aryl boronic acid to palladium, leads to the kinetic (*Z*)-allylpalladium intermediate, which, due to arising $A_{1,2}$-strain, does not isomerize.

Intramolecular carbonyl addition then occurs by way of a 6-centered transition structure where steric interactions with the chiral ligand are minimized.

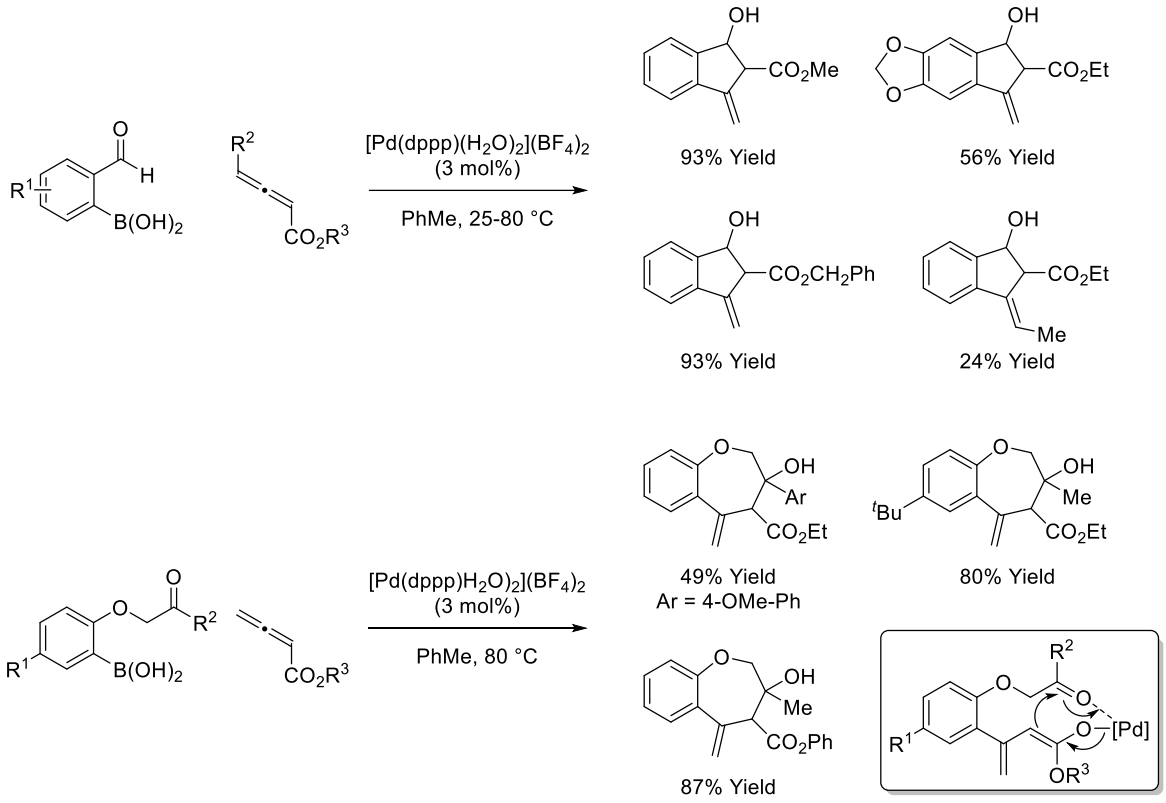
Scheme 1.17 Palladium-Catalyzed Arylative Cyclization of Allenyl Aldehydes with Arylboronic Acids



In 2009, Lu and coworkers[33] described a cationic palladium(II)-catalyzed coupling of 2-formylarylboronic acids and allenoates (Scheme 1.18). Palladium catalysts modified by the achiral bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) and non-coordinating tetrafluoroborate ligands were identified to effectively catalyze the tandem annulation reaction to yield indenol derivatives in good yields as single diastereomers. Efforts toward the asymmetric variant of this reaction identified (*R*)-Tol-BINAP and (*S*)-Tol-SUNPHOS to induce moderate levels of enantioselectivity however, levels of chiral induction were highly substrate dependent (not shown). In a subsequent report, related reactions conditions allowed the formation of 1-benzoxepine derivatives.[34] Utilizing 5-substituted-2-acylmethoxyarylboronic acids and allenoates, products of the tandem annulation could be achieved in good yields as single diastereomers. The catalytic mechanism of these transformations is postulated to involve formation of an arylpalladium intermediate by way of transmetalation, followed by carbopalladation of the internal alkene of the allene due to coordination with the ester carbonyl. Addition to the carbonyl then

likely occurs via the *O*-bound palladium species (Scheme 1.18, bottom right). Protonation of the resulting tertiary palladium alkoxide releases the product alcohol and primes the cationic palladium center for transmetalation.

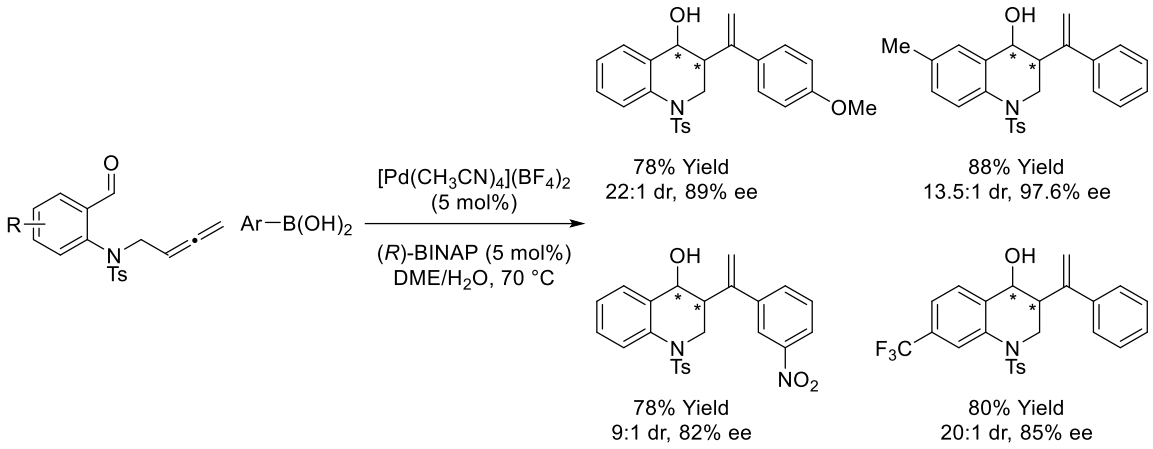
Scheme 1.18 Cationic Palladium(II)-Catalyzed Tandem Annulation of Carbonyl-Containing Boronic Acids and Allenoates



Han, Lu, and co-workers[35] reported another example of arylative cyclization using *N*-tosyl-aniline tethered allenyl aldehydes to synthesize tetrahydroquinoline derivatives (Scheme 1.19). Here, cationic palladium(II) complexes modified by (*R*)-BINAP are effective catalysts for the formation of these 3,4-*cis*-1,2,3,4-tetrahydroquinolines with good to excellent levels of *syn*-diastereo- and enantioselectivity. Again, cationic palladium centers are crucial in these transformations as the non-coordinating anionic ligands provide

a vacant coordination site in the η^1-allylpalladium intermediates, allowing for pre-coordination and activation of the carbonyl.

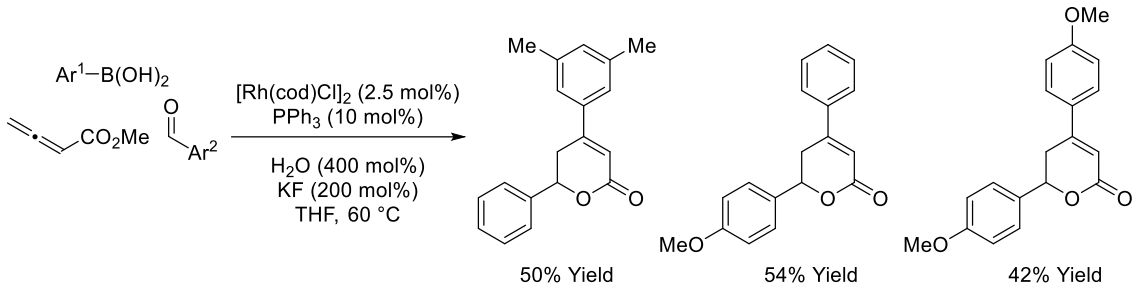
Scheme 1.19 Cationic Palladium(II)-Catalyzed Arylative Cyclization of *N*-Tosyl-Aniline Tethered Allenyl Aldehydes



1.2.3 Rhodium

Ma, Jia, and co-workers[36] reported the rhodium-catalyzed three-component coupling of a methyl allenoate with aryl boronic acids and aldehydes (Scheme 1.20). Utilizing a rhodium(I) precatalyst and triphenylphosphine as ligand, transmetalation from an aryl boronic acid results in the formation of an arylrhodium complex. Subsequent carbometalation of the allenoate and carbonyl addition yield a rhodium alkoxide.

Scheme 1.20 Rhodium-Catalyzed Three-Component Arylboronic Acid–Allene–Aldehyde Coupling

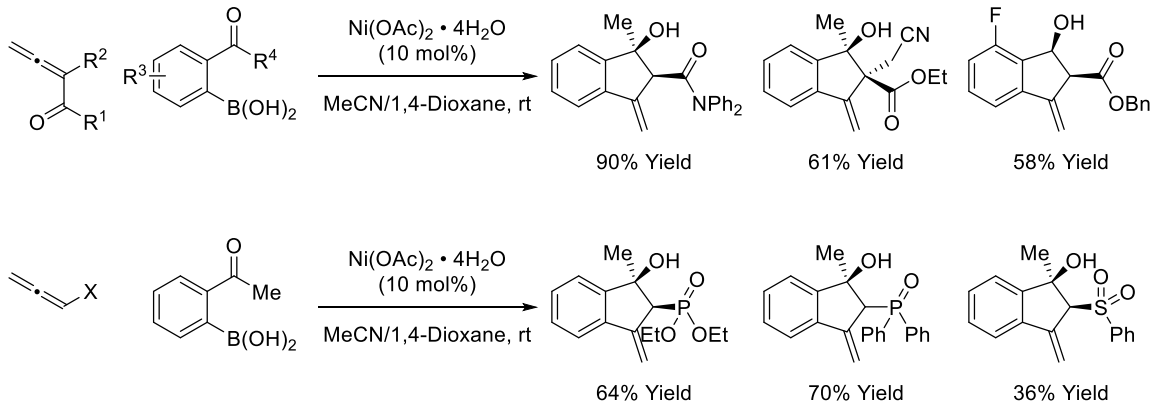


Hydrolysis regenerates the active catalytic species and provides the hydroxyl ester which can then cyclize to form a variety of α,β-unsaturated δ-lactones in moderate yields.

1.2.4 Nickel

In 2018, Lam and co-workers[37] reported the nickel-catalyzed coupling of 2-acetyl- or 2-formylarylboronoic acids with activated allenes (Scheme 1.21). Exploiting [$Ni(OAc)_2 \cdot 4H_2O$], a variety of substituted 3-methyleneindanol products could be isolated in moderate to good yields as single *syn*-diastereomers. In an improvement on prior art, allenes with non-carbonyl substituents such as phosphonates, phosphine oxides, and sulfones, undergo coupling to yield single *syn*-diastereomers with moderate yields (Scheme 1.21). Preliminary studies directed towards the asymmetric variant of this reaction identified a phosphinooxazoline ligand afforded only moderate levels of enantioselectivity when combined with [$Ni(O_2CCF_3)_2 \cdot 4H_2O$] as the nickel precatalyst (not shown).

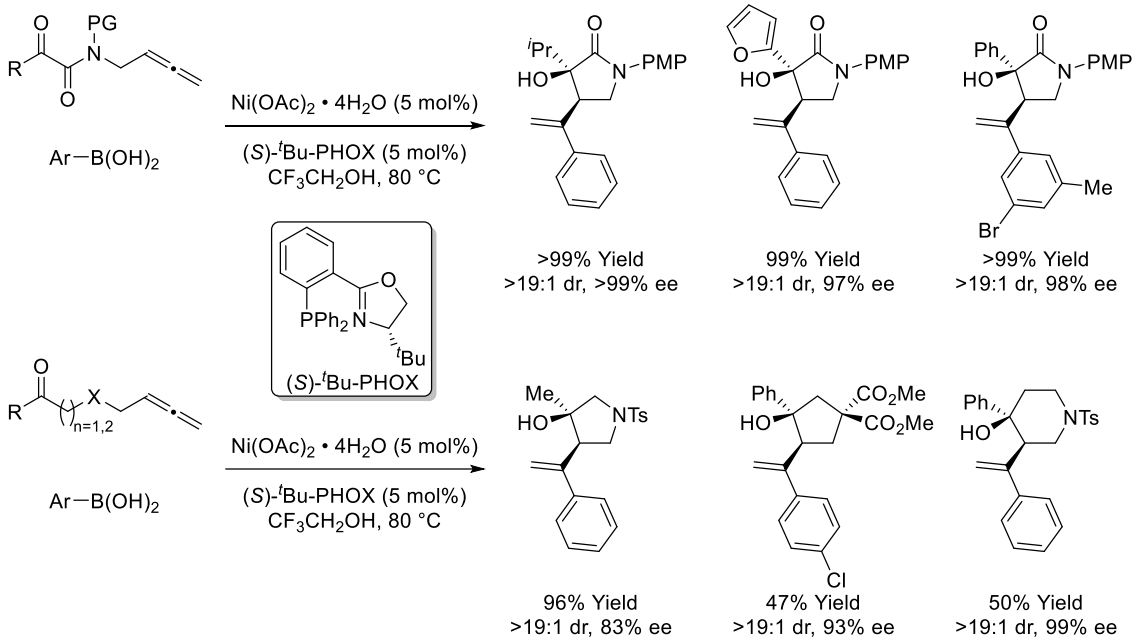
Scheme 1.21 Nickel-Catalyzed Allene–2-Acetylarylboronic Acid Annulation



More recently, Lam and co-workers[38] described the nickel-catalyzed arylative intramolecular allylation of tethered allene–ketones (Scheme 1.22). Utilizing a nickel catalyst modified by the chiral bidentate phosphinooxazoline ligand (*S*)-^{t}Bu-PHOX, coupling tethered allene–α-ketoamides and aryl boronic acids delivered a variety of chiral

pyrrolidine-2-ones with excellent levels of *syn*-diastero- and enantioselectivity. Furthermore, tethered allene–ketones with a variety of tether lengths and heteroatom substitutions afforded aza- and carbocycles in moderate to good yields with excellent levels of *syn*-diastero- and enantioselectivity.

Scheme 1.22 Diastereo- and Enantioselective Nickel-Catalyzed Allylations of Tethered Allene–Ketones

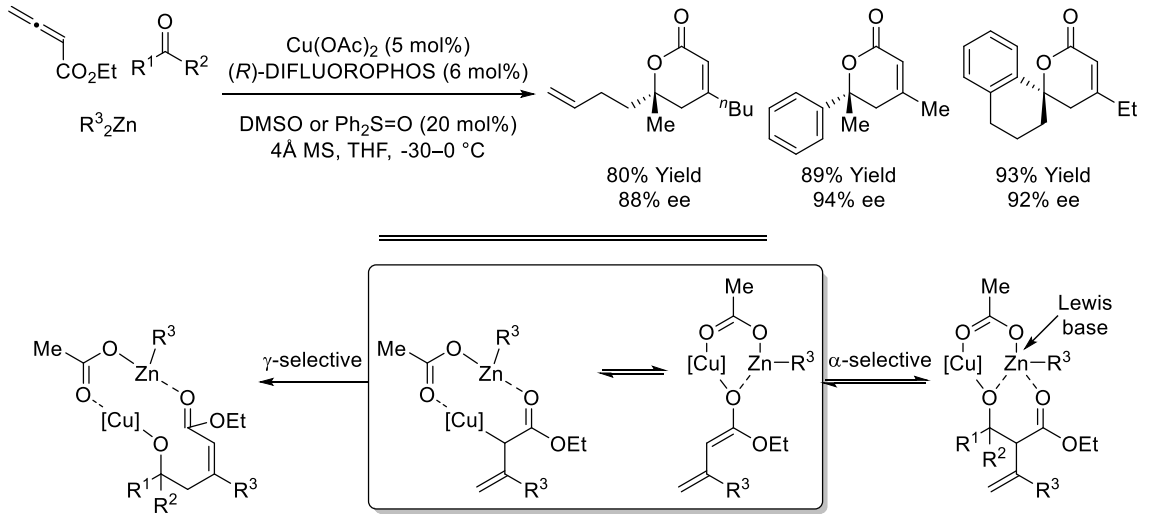


1.2.5 Copper

Copper complexes modified by the chiral bidentate phosphine ligand (*R*)-DIFLUOROPHOS were identified by Kanai, Shibasaki, and co-workers[39] as effective catalysts for the coupling of an ethyl allenoate with dialkylzincs and unactivated ketones (Scheme 1.23). Utilizing dimethyl or diphenyl sulfoxide as Lewis basic additives and molecular sieves, α,β-unsaturated δ-lactone products were formed in good yields with moderate to high levels of enantioselectivity. The proposed catalytic mechanism is postulated to occur by reduction of $Cu(OAc)_2$ with dialkylzinc to form the active

alkylcopper(I) species. Ester-directed carbometalation of the allene results in a copper homoenolate, which is in equilibrium with the copper enolate. Ketone addition results in formation of an aldolate with either α- or γ-selectivity (Scheme 1.23, bottom). The γ-aldolate then undergoes lactonization to release the product and give a copper ethoxide. Interaction with another equivalent of dialkylzinc and molecular sieves forms the alkylcopper(I) species, regenerating the catalytic cycle. The use of Lewis basic additives is postulated to facilitate the reverse reaction of the α-selective reaction allowing consumption of material via the γ-selective pathway.

Scheme 1.23 Enantioselective Copper-Catalyzed Three-Component Dialkylzinc–Allene–Ketone Coupling

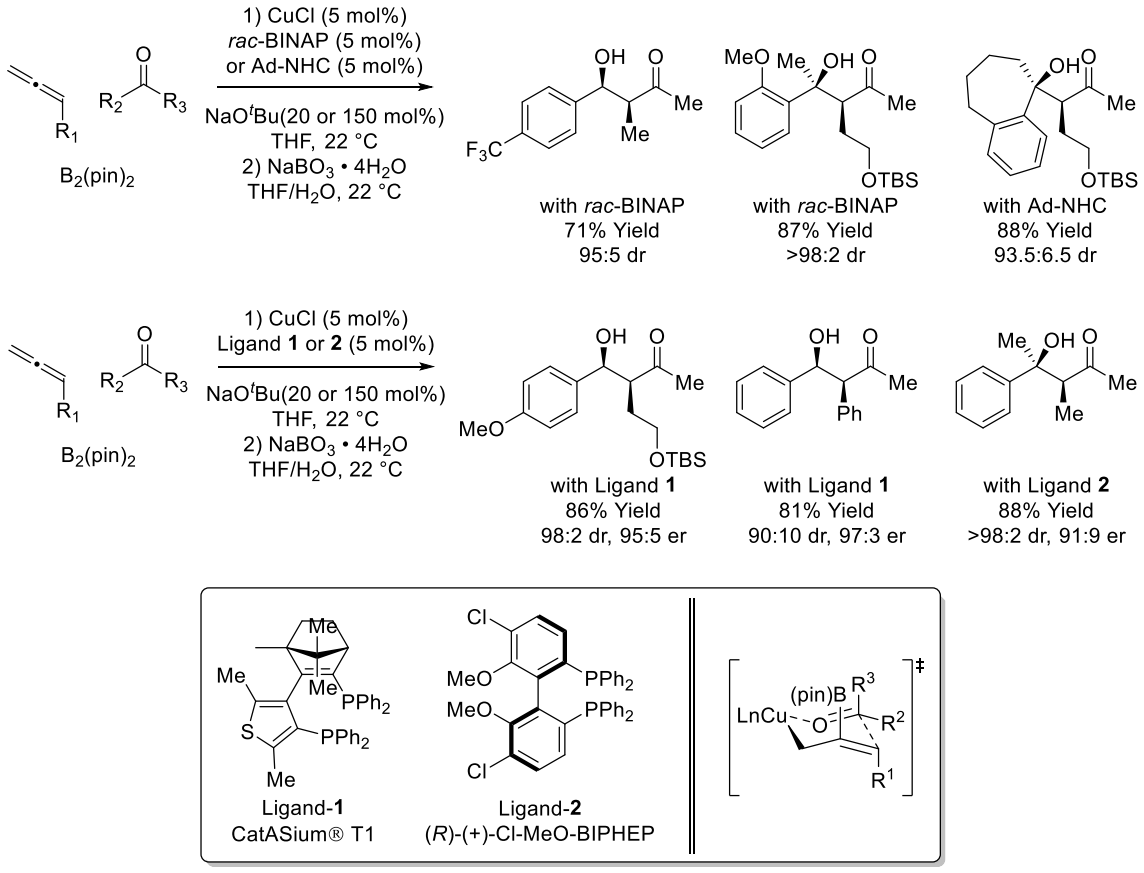


1.4 BOROMETALATIVE PROCESSES

1.4.1 Copper

In 2016, Hoveyda and coworkers[40] reported a copper-catalyzed three-component coupling of bis(pinacolato)diboron [$B_2(pin)_2$], monosubstituted allenes, and aldehydes or ketones (Scheme 1.24). Utilizing either *racemic*-BINAP or the commercially available

Scheme 1.24 Copper-Catalyzed Borylative Aldehyde or Ketone Allylation Followed by C–B Oxidation

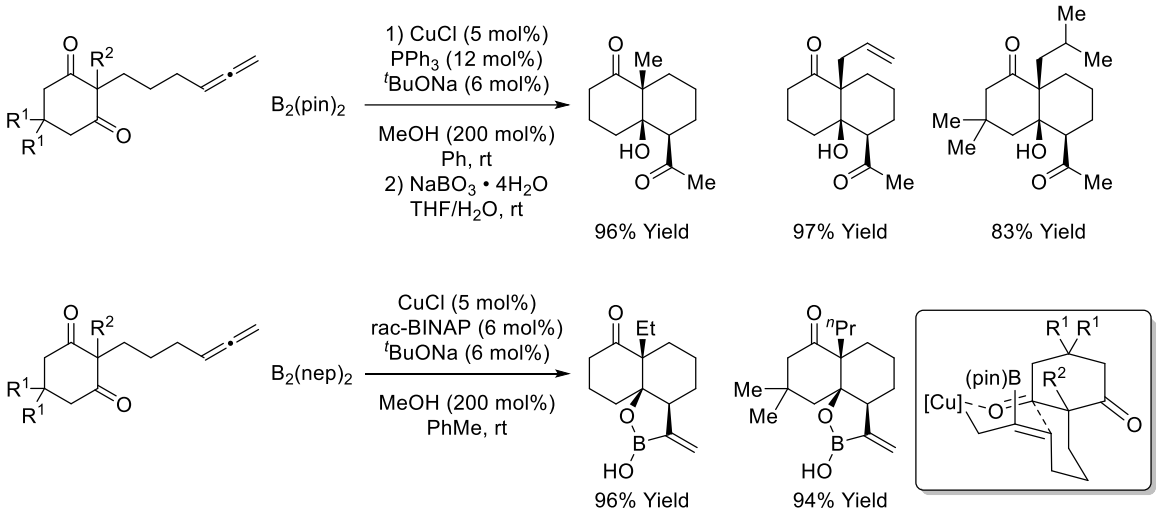


NHC ligand salt 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate (Ad-NHC), racemic β-hydroxyketones are produced with high levels of chemo- and *syn*-diastereoselectivity, following oxidative workup of the 2-B(pin)-substituted homoallylic alkoxides. In the same report, efforts towards the enantioselective variant were also described (Scheme 1.23, bottom). Utilizing CatASium® T1 for aldehydes and (*R*)-(+)-Cl-MeO-BIPHEP for ketones, moderate to good levels of enantioselectivity could be obtained. In both cases, the intermediate homoallylic alkoxides were isolated after oxidative workup as the β-hydroxyketones. Reaction products could also be isolated as the vinylbromides, following exposure of the substituted homoallylic alkoxide to $CuBr_2$ in methanol solvent. Mechanistically, generation of a copper-boron complex followed by borometalation of the

allene terminus results in a nucleophilic 2-B(pin)-substituted allylcopper intermediate that can undergo carbonyl addition via a closed six-centered transition state (Scheme 24, bottom right).

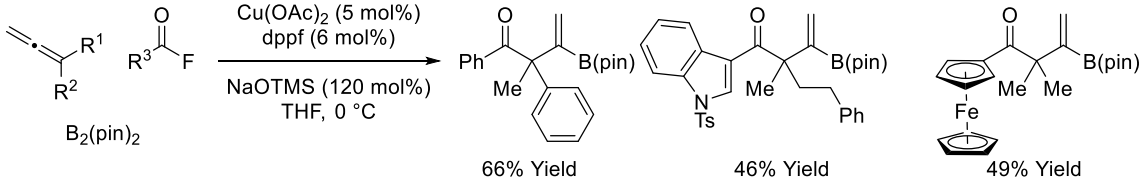
Tao, Tian, and co-workers[41] reported a copper(I)-catalyzed borylative cyclization of tethered allene cyclohexanediones (Scheme 1.25). Copper complexes modified by triphenylphosphine were effective catalysts for the formation of *cis*-decalinols when utilizing [$B_2(pin)_2$] as boron source. The resulting 2-B(pin)-substituted homoallylic alcohols are subjected to oxidative workup yielding ketone-bearing *cis*-decalinol products as single diastereomers in excellent yields. The complementary copper catalyst modified by *racemic*-BINAP effectively catalyzes this transformation utilizing bis(neopentyl glycolato)diboron ([$B_2(nep)_2$]) as boron source to form stable hemiboronates as single *syn*-diastereomers in excellent yields. The catalytic mechanism is postulated to proceed by way of a highly organized 6-centered transition state, accounting for the high levels of diastereoselectivity observed (Scheme 1.25, bottom right).

Scheme 1.25 Copper-Catalyzed Borylative Cyclization of Tethered Allene Cyclohexanediones



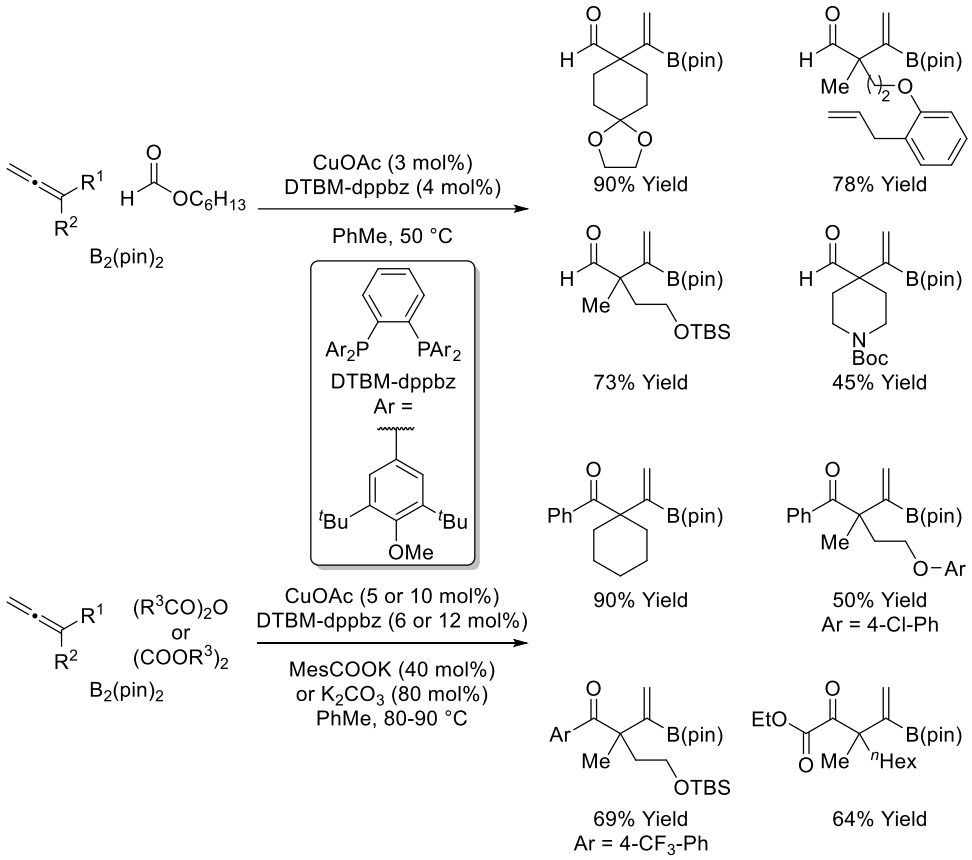
Gagosz, Riant, and co-workers[42] described copper complexes modified by the bidentate phosphine ligand 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf) for the catalytic boroacylation of allenes (Scheme 1.26). Utilizing a variety of acyl fluorides, 1,1-disubstituted allenes, and [$B_2(pin)_2$], β-boryl-β,γ-unsaturated ketones are afforded in moderate to good yields. The catalytic mechanism is postulated to occur by borometalation of the allene terminus by a borylcopper species giving a β-boryl allylcopper intermediate. Carbonyl addition then occurs via a 6-centered transition state followed by β-fluoride elimination to release the product.

Scheme 1.26 Copper-Catalyzed Boroacylation of 1,1-Disubstituted Allenes



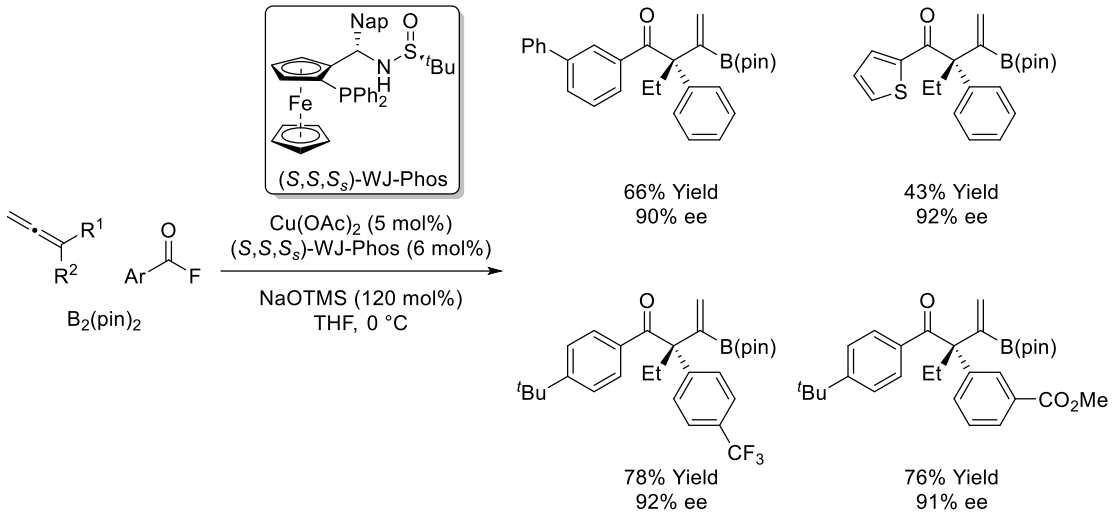
In 2017 Fujihara, Tsuji, and co-workers[43] described a related copper-catalyzed boroformylation of allenes (Scheme 1.27). A variety of 1,1-disubstituted allenes were reacted with hexyl formate and [$B_2(pin)_2$] to form the corresponding β-boryl β,γ-unsaturated aldehydes in good to excellent yields. A later report by the same group utilized similar reaction conditions to effectively generate products of allene boroacylation and boroalkoxyoxalylation employing anhydrides and oxalates, respectively, as carbonyl electrophiles.[44] Mechanistically similar to the previous transformation reported by Gagosz, Riant, and co-workers,[42] following borometalation carbonyl addition occurs by way of a 6-center transition state to give a copper carboxylate. β-Elimination releases the acylation products and generates a copper alkoxide, which then undergoes σ-bond metathesis with [$B_2(pin)_2$] to regenerate the catalytic cycle.

Scheme 1.27 Copper-Catalyzed Boroforymlation, Boroacylation, and Boroalkoxyoxalylation of 1,1-Disubtituted Allenes



An enantioselective variant of these boroacylation reactions employing 1,1-disubstituted allenes and benzoyl fluorides was later described by Zhang and co-workers (Scheme 1.28).[45] Through ligand design and synthesis, a novel class of chiral ligands, deemed WJ-Phos, were identified to form copper complexes that are effective catalysts for the formation of β-boryl-β,γ-unsaturated ketones bearing a quaternary carbon stereocenter in good yields with high levels of enantioselectivity.

Scheme 1.28 Enantioselective Copper-Catalyzed Boroacylation of 1,1-Disubstituted Allenes



1.5 CONCLUSION

The of use of allenes in hydro-, carbo-, and borometalative processes to generate nucleophilic allylmetal intermediates for carbonyl addition provide powerful methods to circumvent the use of preformed carbanion equivalents. Although a significant amount of progress has been achieved, there are still unmet challenges to be overcome. Primarily, several of the described transformations utilize stoichiometric metallic reductants. Furthermore, the use of allenes containing directing or activating substituents, such as esters, is prevalent. Future advancements in this field will likely focus on utilization of organic reductants and unactivated starting materials and the development of more robust catalysts and ligands for selective processes.

Chapter 2: Cyclometalated Iridium–PhanePhos Complexes in the Enantioselective Formation of Acyclic Quaternary Carbon Stereocenters*

2.1 INTRODUCTION

The catalytic enantioselective formation of all-carbon quaternary stereocenters remains a formidable challenge in chemical synthesis.[1–3] Diverse catalytic enantioselective methods enabling formation of quaternary carbon stereocenters that reside within cyclic frameworks have been reported.[1] In contrast, catalytic enantioselective methods that deliver acyclic quaternary carbon stereocenters remain relatively uncommon.[1d,k,4,5] In the course of developing catalytic enantioselective carbonyl reductive couplings via alcohol-mediated hydrogen transfer or hydrogen auto-transfer,[6] the Krische group recently developed enantioselective methods for the formation of acyclic quaternary carbon stereocenters that operate under non-cryogenic conditions and are completely atom-efficient, bypassing the use of stoichiometric metals.[3] In these processes, vinyl epoxides[3a,b,d] and 1,3-dienes[3c] as serve as pronucleophiles.

* This chapter is based on the previously published works:

1) Holmes, M. T.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. Enantioselective Formation of CF_3-Bearing All-Carbon Quaternary Stereocenters via C-H Functionalization of Methanol: Iridium Catalyzed Allene Hydrohydroxymethylation. *J. Am. Chem. Soc.* **2017**, *139*, 8114.
2) Schwartz, L. A.; Holmes, M. T.; Brito, G. A.; Goncalves, T. P.; Richardson, J.; Ruble, J. C.; Huang, K. -W.; Krische, M. J. Cyclometallated Iridium-PhanePhos Complexes Are Active Catalysts in Enantioselective Allene-Fluoral Reductive Coupling and Related Alcohol-Mediated Carbonyl Additions that Form Acyclic Quaternary Carbon Stereocenters. *J. Am. Chem. Soc.* **2019**, *141*. 2087

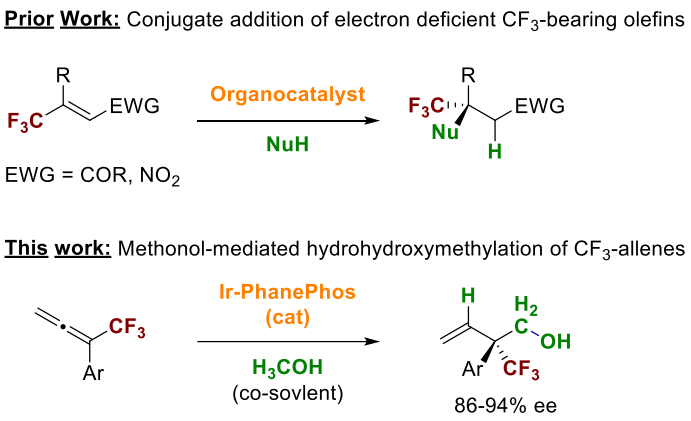
L.A.S contributed to reaction discovery and optimization (Table 2.1; Figure 2.2), substrate scope (Tables 2.2–2.4), kinetic and mechanistic studies (Figures 2.3 – 2.5; Scheme 2.5), and preparation of manuscript and supporting information.

2.2 Iridium Catalyzed Allene Hydrohydroxymethylation

2.2.1 Background

The enantioselective formation of acyclic CF_3-bearing all-carbon quaternary centers is an especially daunting challenge.[7–10] As established in seminal work by Shibata,[7a] methods capable of delivering this motif are restricted to conjugate additions of β,β-disubstituted enones[7a,b,e,g,h] or nitroolefins[7c,d,f,i–k] and two isolated reports of asymmetric allyl[8a] and propargyl[8b] substitution (Scheme 2.1). Attempts to adapt previously developed technology from the Krische group to the formation of acyclic CF_3-bearing stereocenters via ruthenium catalyzed CF_3-allene-paraformaldehyde reductive coupling mediated by 2-propanol failed to deliver highly enantiomerically enriched adducts.[11] The unique efficacy of iridium-PhanePhos[12] complexes in previously developed methanol mediated hydrohydroxymethylations of 2-substituted-1,3-dienes,[3c] along with the availability of improved protocols for the preparation of CF_3-allenes,[13] motivated continued efforts toward this elusive bond formation. Expanding upon the use of methanol as a C1-feedstock in metal catalyzed C–C coupling,[14–16] iridium-PhanePhos complexes

Scheme 2.1 Catalytic Enantioselective Formation of Acyclic CF_3-bearing All-Carbon Quaternary Stereocenters



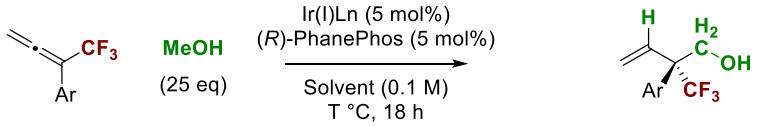
were utilized to promote the methanol-mediated hydrohydroxymethylation of CF_3-allenes to form highly enantiomerically enriched adducts with complete branched regioselectivity (Scheme 2.1). Thus, catalytic enantioselective formation of acyclic CF_3-bearing all-carbon quaternary stereocenters is achieved in the absence of stoichiometric metals or byproducts.

2.2.2 Reaction Development and Scope

Given the singular effectiveness of iridium-PhanePhos in asymmetric diene hydrohydroxymethylation,[3c] these conditions were applied to the coupling of methanol with 1,1-disubstituted CF_3-allenes 2.1[a−o]. Although the desired coupling products 2.2[a−o] were generated with complete branched regioselectivity, the reaction was highly substrate dependent with significant variation in isolated yield and enantioselectivity. Furthermore, all other chiral ligands that were evaluated failed to deliver products of C−C coupling. These circumstances led us to explore the influence of alternate reaction parameters. As illustrated in the optimization of the methanol-mediated hydrohydroxymethylation of CF_3-allene **2.1i** to form **2.2i**, several interesting trends emerged (Table 2.1). For CF_3-allene **2.1i** and other allenes bearing electron deficient aryl moieties, changing the precatalyst from $[Ir(cod)Cl]_2$ to Ir(cod)(acac) resulted in higher levels of enantiomeric enrichment, but with lower conversion (Table 2.1, entries 2 and 3). A modest increase in reaction temperature improved the isolated yield of **2.2i** without compromising enantioselectivity (Table 2.1, entry 4). The addition of water (500 mol %) increased enantioselectivity, but led to competing transfer hydrogenation of **2.1i** (Table 1, entry 5). Tetrabutylammonium iodide (TBAI) (10 mol %) suppresses competing transfer hydrogenation and increases enantioselectivity to a small extent (Table 1, entry 6). Using water (500 mol %) and TBAI (10 mol %) in concert, the neopentyl alcohol **2.2i** could be

obtained in 81% yield and 90% ee (Table 2.1, entry 7). Exchanging acetone for ethyl acetate as solvent improved enantioselectivity but diminished yield (Table 2.1, entry 8).

Table 2.1. Optimization of the Enantioselective Iridium-Catalyzed C–C Coupling of CF_3-Allenes with Methanol[a]



2.1d, Ar = 3-OMe-Ph
or **2.1i**, Ar = 3-NO_2-Ph
(100 mol%)

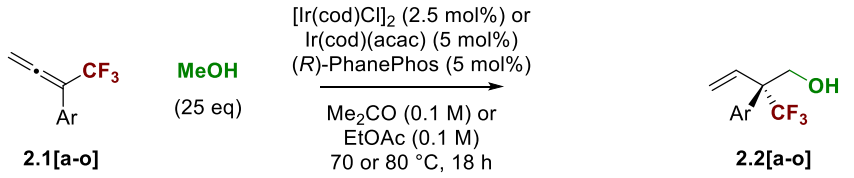
2.2d or **2.2i**

Entry	Ar =	Ir(I)L_n	Additive	Solvent	T (°C)	Yield (%)	ee (%)
⇨1	3-OMe-Ph	$[Ir(cod)Cl]_2$	-	Me_2CO	70	84	90
2	3-NO_2-Ph	$[Ir(cod)Cl]_2$	-	Me_2CO	70	56	64
3	3-NO_2-Ph	Ir(cod)(acac)	-	Me_2CO	70	14	79
4	3-NO_2-Ph	Ir(cod)(acac)	-	Me_2CO	80	79	79
5	3-NO_2-Ph	Ir(cod)(acac)	H_2O (500 mol%)	Me_2CO	80	56	89
6	3-NO_2-Ph	Ir(cod)(acac)	TBAI (10 mol%)	Me_2CO	80	79	84
7	3-NO_2-Ph	Ir(cod)(acac)	H_2O/TBAI	Me_2CO	80	81	90
⇨8	3-NO_2-Ph	Ir(cod)(acac)	H_2O/TBAI	EtOAc	80	72	94

[a]Yields of material isolated by silica gel chromatography. Enantiose-lectivities were determined by chiral stationary phase HPLC analysis.

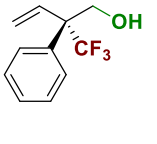
Taking into account the aforesaid influence of the indicated reaction parameters, the conversion of 1,1-disubstituted CF_3-allenes **2.1[a−o]** to neopentyl alcohols **2.2[a−o]** was explored (Table 2.2). Two general sets of conditions emerged. In the coupling of CF_3-allenes **2.1[a−f]** and **2.1k**, which incorporate electron rich, electron neutral or slightly electron deficient aryl moieties, use of the iridium catalyst derived from $[Ir(cod)Cl]_2$ and (*R*)-PhanePhos in acetone solvent at 70 °C was optimal. For CF_3-allenes bearing highly electron deficient aryl moieties, the precatalyst Ir(cod)(acac) in ethyl acetate solvent at 80 °C was preferred. Under both sets of conditions, TBAI and H_2O were frequently required to enhance enantioselectivity. By tailoring reaction conditions in this manner, alcohols **2.2[a−o]** with CF_3-bearing all-carbon quaternary stereocenters could be formed with uniformly high levels of enantioselectivity and as single regioisomers. Alkyl substituted CF_3-allenes engage in efficient methanol-mediated hydrohydroxymethylation, but enantio-

Table 2.2. Enantioselective Iridium-Catalyzed Coupling of Methanol with CF_3-Allenes **2.1[a-o]** To Form Higher Alcohols **2.2[a-o]**[a]

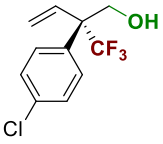


2.1[a-o] **2.2[a-o]**

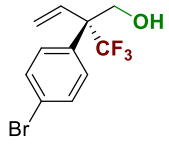
2.1a, Ar = Ph	**2.1b**, Ar = 4-Cl-Ph	**2.1c**, Ar = 4-Br-Ph	**2.1d**, Ar = 4-MeO-Ph
2.1e, Ar = 3-MeO-Ph	**2.1f**, Ar = 5-benzodioxole	**2.1g**, Ar = 4-CO_2Me-Ph	**2.1h**, Ar = 4-CF_3-Ph
2.1i, Ar = 3-NO_2-Ph	**2.1j**, Ar = 3,5-F_2-Ph	**2.1k**, Ar = 5-(2-MeO-Pyr)	**2.1l**, Ar = 5-indanone
2.1m, Ar = 4-CF_3S-Ph	**2.1n**, Ar = 3-NO_{2-4}-MeO-Ph	**2.1o**, Ar = 3,5-Cl_2-Ph	



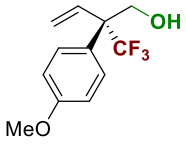
2.2a
75% Yield, 87% ee[b]
95% Yield, 90% ee[b,d]



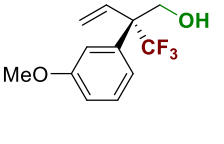
2.2b
77% Yield, 86% ee[b]
62% Yield, 90% ee[b,f]
(X-ray)



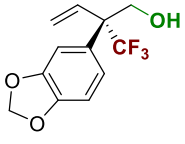
2.2c
79% Yield, 87% ee[b]
60% Yield, 91% ee[b,f]



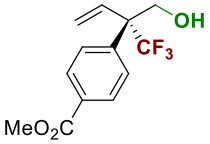
2.2d
90% Yield, 89% ee[b]
93% Yield, 90% ee[b,d]



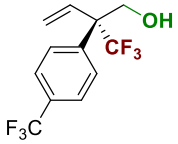
2.2e
84% Yield, 90% ee[b]



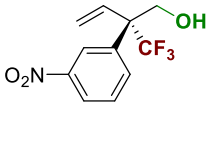
2.2f
79% Yield, 90% ee[b,d]
(X-ray)



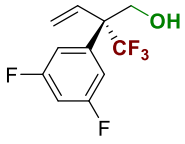
2.2g
59% Yield, 92% ee[c,e]



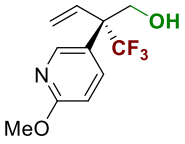
2.2h
64% Yield, 90% ee[c,e]



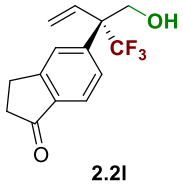
2.2i
72% Yield, 94% ee[c,f]



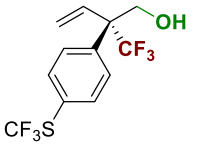
2.2j
69% Yield, 91% ee[c,e]



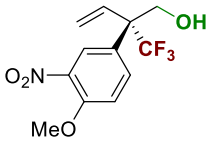
2.2k
80% Yield, 84% ee[b]
71% Yield, 89% ee[b,f]



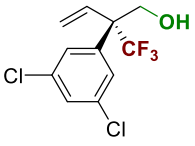
2.2l
81% Yield, 89% ee[c,e]
59% Yield, 92% ee[c,f]



2.2m
58% Yield, 91% ee[c,f]



2.2n
73% Yield, 94% ee[c,f]



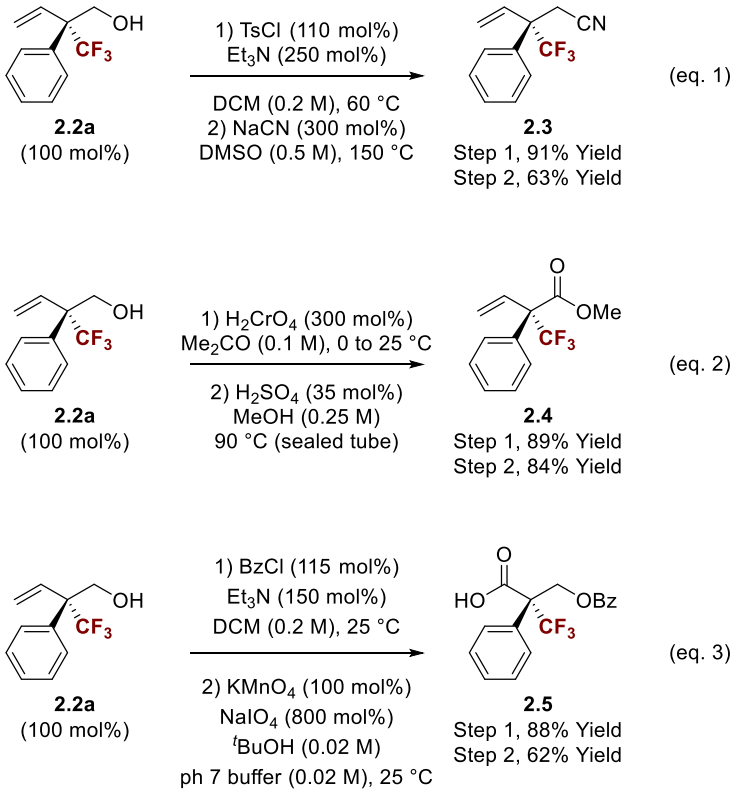
2.2o
57% Yield, 90% ee[c,f]

[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis.[b][Ir(cod)Cl]$_2$,70°C, Me_2CO.[c]Ir(cod)(acac), TBAI (10 mol %), 80°C, EtOAc.[d]TBAI (10 mol %).[e]H_2O (200 mol %).[f]H_2O (500 mol%).

selectivities were lower (<50% ee). The absolute stereochemical assignment of adducts **2.2[a−o]** is based on single crystal X-ray diffraction analysis of **2.2b** and **2.2f**. Attempted use of higher alcohols led to regio- and enantioselective transfer hydrogenation of the internal allene π-bond (ca. 40% ee).

To demonstrate how adducts **2.2[a−o]** can be used in chemical synthesis, alcohol **2.2a** was subjected to a series of functional group manipulations. Conversion of alcohol **2.2a** to the corresponding *p*-toluenesulfonate followed by exposure to sodium cyanide in DMSO at 150 °C provided the nitrile **2.3**, representing a remarkable example of an S_N2 reaction at a highly congested neopentyl center (Scheme 2.2, eq. 1). Jones oxidation of alcohol **2.2a** followed by Fischer esterification provides the β,γ-unsaturated methyl ester

Scheme 2.2 Functional Group Manipulations of Adduct **2.2a**



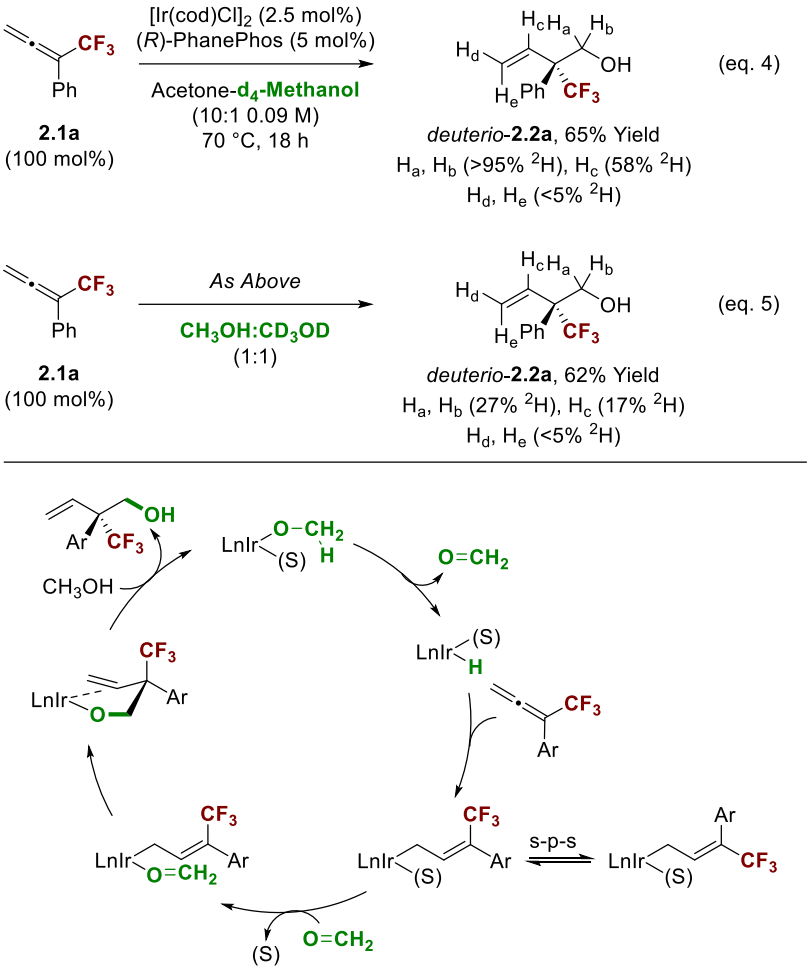
2.4 (Scheme 2.2, eq. 2). Finally, conversion of alcohol **2.2a** to the benzoate followed by oxidative cleavage[17] of the vinyl moiety delivers the chiral α-stereogenic carboxylic acid **2.5** (Scheme 2.2, eq. 3).

2.2.3 Mechanism and Discussion

As exemplified in methanol-mediated transfer hydrogenations of C−C π-bonds,[18] the reversible and highly endothermic nature of methanol dehydrogenation ($\Delta H_{(MeOH)}$ = +20 kcal/mol vs $\Delta H_{(EtOH)}$ = +16 kcal/mol)[19] can be overcome by linking dehydrogenation to an exothermic process. Methanol dehydrogenation also poses a significant challenge in the hydrohydroxymethylation of π-unsaturated reactants and invariably represents the rate-limiting step.[3c,16] However, as the present allene-methanol C−C couplings involve formation of a highly congested CF_3-bearing all-carbon quaternary stereocenter, it was unclear whether methanol dehydrogenation or carbonyl addition would be rate-limiting.

To gain further insight into the catalytic mechanism, CF_3-allene **2.1a** was subjected to d_4-methanol under otherwise standard conditions (Scheme 2.3, eq. 4). The product, *deuterio*-**2.2a**, completely retains deuterium at the carbinol position (H_a, H_b = >95% ^2H), suggesting *deuterio*-**2.2a** is kinetically inert with respect to dehydrogenation due to coordination of the homoallylic olefin to iridium, blocking the adjacent coordination site required for β-hydride elimination. Although deuterium is not incorporated at the vinylic terminus of *deuterio*-**2.2a** (H_d, H_e = <5% ^2H), a significant quantity of deuterium appears at the internal vinylic position (H_c = 58% ^2H). Unlike related diene methanol C−C couplings,[3c] this data suggests the hydrometallation event is a completely regioselective process. Incomplete incorporation of deuterium at the internal vinylic position may be due to adventitious water.[19,20] In a related competition kinetics experiment, CF_3-allene **2.1a** was

Scheme 2.3 Deuterium Labelling Studies and Catalytic Mechanism[a]



[a]Yields of material isolated by silica gel chromatography. The extent of deuterium incorporation was determined by HRMS and ^{1}H and ^{2}H NMR analysis.

exposed to equimolar quantities of methanol and *d*$_4$-methanol under otherwise standard conditions (Scheme 2.3, eq. 5). Deuterium incorporation at the carbinol methylene (H_a, H_b = 27% ^{2}H) ofthe product *deuterio*-**2.2a** constitutes a normal primary kinetic isotope effect ($k_H/k_D \approx 3.0$) consistent with turnover-limiting methanol dehydrogenation. The influence of the precatalyst and additives (TBAI, H_2O) on enantioselectivity suggest the counterion (and water) are present during the enantiodetermining carbonyl addition event. To

accommodate this observation, we propose that carbonyl addition occurs from an allyliridium-(III) intermediate (Scheme 2.3, bottom).

2.2.4 Conclusion

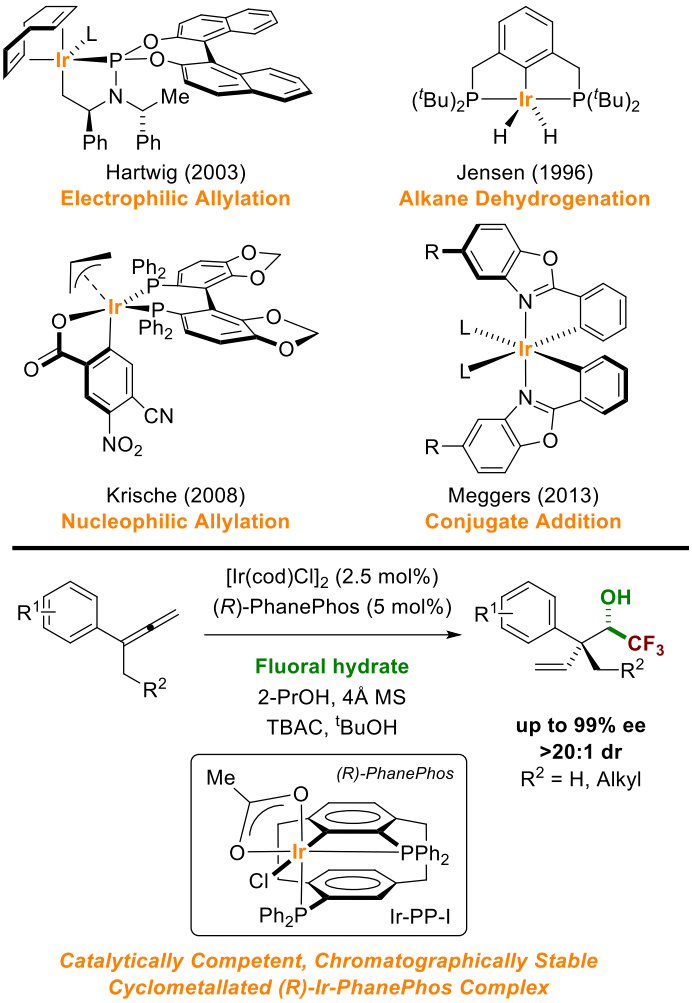
In conclusion, CF_3-bearing all-carbon quaternary stereocenters are exceptionally difficult to prepare in enantiomerically enriched form, with previous protocols for their construction largely restricted to conjugate additions to β,β-disubstituted CF_3-enones and nitroolefins.[7] It has been demonstrated that iridium complexes modified by PhanePhos catalyze the methanol-mediated hydrohydroxymethylation of CF_3-allenes to generate this structural motif in a completely regioselective and highly enantioselective fashion in the absence of stoichiometric metals or byproducts.

2.3 Enantioselective Allene–Fluoral Reductive Coupling and Identification of Cyclometalated Iridium–PhanePhos Complex

2.3.1 Background

While the formation of acyclic quaternary carbon stereocenters is a difficult challenge in chemical synthesis.[1-3] Even more elusive are asymmetric methods that deliver (a) acyclic quaternary carbon-containing stereopolyads[5] or (b) fluorinated acyclic quaternary carbon-containing structural motifs.[9h–l,n,p-s,21] As previously discussed, iridium complexes modified by the chiral phosphine ligand PhanePhos[12] were uniquely effective in catalyzing highly regio- and enantioselective methanol-mediated formaldehyde additions.[3c,14,22] Other chelating phosphine ligands were completely inactive in these processes. The singular effectiveness of the iridium−PhanePhos catalyst prompted further exploration of its capabilities and investigations into the precise nature of the catalytically active species. It was discovered that the iridium complex derived from $[Ir(cod)Cl]_2$ and PhanePhos catalyzes highly regio-, diastereo- and enantioselective allene−fluoral reductive couplings mediated by 2-propanol to form acyclic quaternary carbon-containing stereodiads.[11,15,23−26] Of greater significance, these studies led to the identification of a cyclometalated iridium−PhanePhos complex that is catalytically competent – not only in the present transformation but also in previously reported iridium−PhanePhos-catalyzed reactions developed in our laboratory.[3c,22] This complex contributes to a growing collection of cyclometalated iridium complexes that display diverse catalytic activities (Figure 2.1).[27]

Figure 2.1 Diverse catalytic activities of cyclometalated iridium complexes and the identification of a catalytically competent cyclometalated iridium–PhanePhos complex.



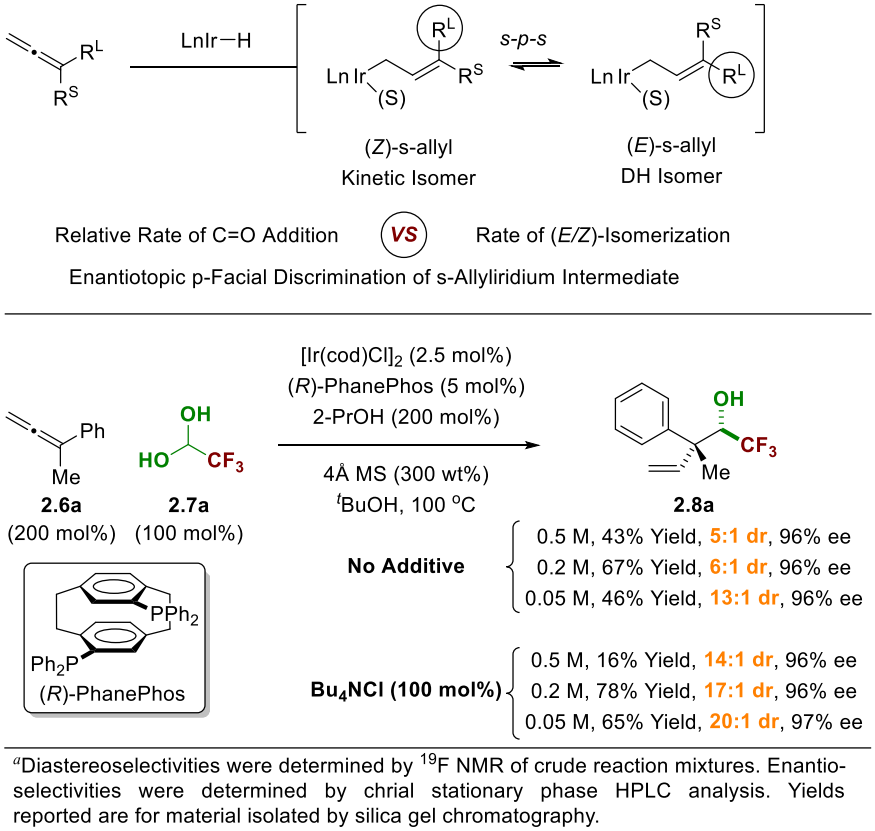
2.3.2 Reaction Development and Scope

Prior work on enantioselective iridium–PhanePhos-catalyzed C–C coupling focused on methanol-mediated formaldehyde additions.[3c,22] Steric issues posed by the formation of a more highly substituted quaternary carbon C–C bond prohibited reactions of higher aldehydes. It was posited that fluoral, a highly reactive carbonyl electrophile like formaldehyde, might participate in alcohol-mediated reductive coupling to provide acyclic

quaternary carbon stereodiads incorporating a trifluoroethyl carbinol fragment.[28] However, the feasibility of allene–fluoral reductive coupling was rendered uncertain by two issues. First, fluoral is only commercially available as the hydrate or hemiacetal, yet the vast majority of enantioselective metal-catalyzed fluoral additions require use of anhydrous fluoral.[9h–s,21] Second, high levels of stereoselectivity require not only discrimination of enantiotopic carbonyl π-faces, but also intervention of a single geometrical isomer of the σ-allyliridium nucleophile. The latter issue is further complicated by the fact that hydroiridation of 1,1-disubstituted allenes occurs preferentially at the allene π-face proximal to the smaller allene substituent (R_s) to furnish the less stable (*Z*)-σ-allyliridium isomer. Hence, notwithstanding Curtin–Hammett effects,[29] in order to form the quaternary carbon stereocenter with optimal levels of stereoselectivity, either kinetic stereoselectivity favoring formation of the (*Z*)-σ-allyliridium isomer must be preserved or equilibration between the (*Z*)- and (*E*)-σ-allyliridium isomers must be achieved prior to carbonyl addition with complete conversion to the latter (Figure 2.2, top). The difference in energy between (*Z*)- and (*E*)-2-phenyl-2-butenes is more than 1 kcal/mol, and greater energetic differentiation is anticipated for the corresponding (*Z*)- and (*E*)-σ-allyliridium species.[30]

With these considerations in mind, the following series of experiments was performed (Figure 2.2, bottom). Allene **2.6a** (200 mol%), fluoral hydrate **2.7** (100 mol%, 75 wt% in water), and 2-propanol (200 mol%) were exposed to the iridium catalyst derived from $[Ir(cod)Cl]_2$ (2.5 mol%) and (*R*)-PhanePhos (5 mol%) in tert-butanol (0.5 M) at 100 °C. In the absence of desiccant, only a trace quantity of the targeted reductive coupling product **2.8a** was observed. However, upon addition of 4Å molecular sieves, compound **2.8a** was formed in 43% yield as a 5:1 mixture of diastereomers in 96% enantiomeric excess. In accord with our stereochemical analysis, it was reasoned that more dilute conditions might increase diastereoselectivity by decreasing the rate of carbonyl addition

Figure 2.2 Relative and Absolute Stereoselection in 2-Propanol-Mediated Reductive Couplings of Allenes with Fluoral Hydrate via Concentration-Dependent Diastereoselectivity



[a]Diastereoselectivities were determined by ^{19}F NMR of crude reaction mixtures. Enantioselectivities were determined by chrial stationary phase HPLC analysis. Yields reported are for material isolated by silica gel chromatography.

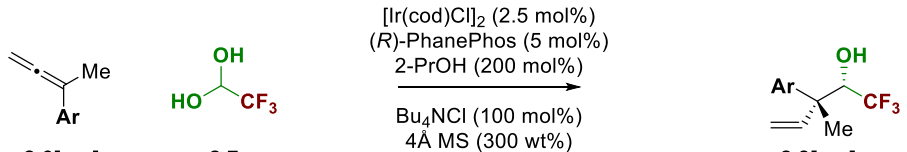
with respect to the rate of equilibration between the (*Z*)- and (*E*)-σ-allyliridium isomers.[29] Indeed, in the event, diastereoselectivity was found to increase with increasing dilution, and at 0.05 M a 13:1 diastereomeric ratio was observed without any erosion of enantioselectivity, although under these dilute conditions the isolated yield of **2.8a** suffered. In the course of our optimization experiments, we also observed that more Lewis basic solvents promote higher diastereoselectivities. This fact led us to explore the effect of halide additives. To our delight, introduction of Bu_4NCl (100 mol%) not only improved diastereoselectivity, but also increased the isolated yield of **2.8a**. At 0.2 M in the presence of Bu_4NCl, compound **2.8a** was formed in 78% yield as a 17:1 mixture of diastereomers with a 96% enantiomeric excess. Diastereoselectivity remained constant at 80, 90 and 100

°C, and at lower temperatures conversion decreased precipitously, so diastereoselectivity was not calculated.

These optimized conditions were applied to the reductive coupling of 1,1-disubstituted allenes **2.6[a−o]** bearing aryl and methyl groups with fluoral hydrate **2.7** (Table 2.3). Allenes **2.6[b−k]** bearing aryl moieties with diverse substitution patterns and electronic properties are converted to adducts **2.8[b−k]** in good yield with uniformly high levels of regio-, diastereo- and enantioselectivity. Notably, functional groups that are potentially susceptible to reduction, for example nitro groups (**2.8j**) and ketones (**2.8k**), remain intact. Heteroaryl-substituted allenes **2.6[l−o]** are also effective partners for reductive coupling, providing adducts **2.8[l−o]** with high levels of relative and absolute stereocontrol. For N-heterocycles, at least one ortho-substituent adjacent to nitrogen is required for high levels of conversion.

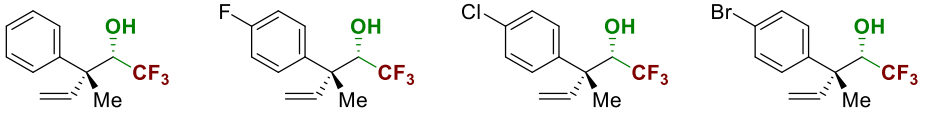
To test the limits of stereoselectivity, 1,1-disubstituted allenes **2.6[p−u]** bearing higher alkyl substituents were evaluated in reductive couplings to fluoral **2.7** (Table 2.4). Remarkably, although increasing size of the alkyl moiety was anticipated to erode partitioning of the transient (*E*)- and (*Z*)-σ-allyliridium isomers, excellent levels of stereocontrol were retained in reactions of allenes **2.6[p−u]** that incorporate linear alkyl groups. In contrast, attempted reactions of allenes bearing branched alkyl groups, for example, cycloalkyl moieties, were low-yielding and non-diastereoselective. The absolute stereochemical assignment of all adducts **2.8[a−u]** is made in analogy to that established for the 3,5-dinitrobenzoate of **2.8d**, which was determined by single-crystal X-ray diffraction analysis.

Table 2.3 Iridium-Catalyzed Coupling of Allenes **2.6[a-o]** with Fluoral Hydrate **2.7** To Form Adducts **2.8[a-o]** Bearing Acyclic Quaternary Carbon Stereocenters[a]



2.6[a-o] (200 mol%) | **2.7** (100 mol%) | **2.8[a-o]**

2.6a, Ar = Ph	**2.6b**, Ar = 4-F-Ph	**2.1c**, Ar = 3-Cl-Ph	**2.6d**, Ar = 4-Br-Ph
2.6e, Ar = 4-MeO-Ph	**2.6f**, Ar = 3-NHAc-Ph	**2.1g**, Ar = 3-MeO-Ph	**2.6h**, Ar = 3,5-Cl_2-Ph
2.6i, Ar = 2-F-Ph	**2.6j**, Ar = 3-NO_2-Ph	**2.1k**, Ar = 4-COMe-Ph	**2.6l**, Ar = 3-Thienyl
2.6m, Ar = 5-(2-MeO-Pyr)	**2.6n**, Ar = 5-(2-Me-Pym)	**2.1o**, Ar = 4-(6-MeO-Quin)	

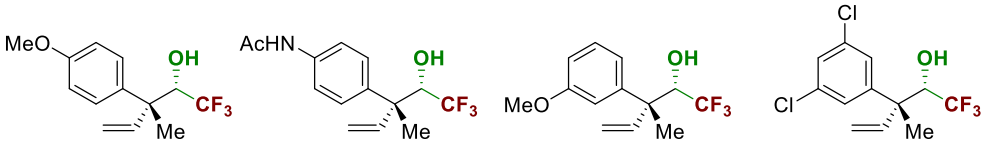


2.8a
75% Yield
17:1 dr, 96% ee

2.8b
81% Yield
19:1 dr, 96% ee

2.8c
72% Yield
18:1 dr, 96% ee

2.8d
85% Yield
19:1 dr, 96% ee
(2 mmol scle, X-ray)

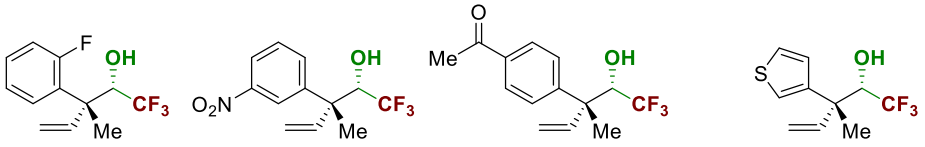


2.8e
79% Yield
14:1 dr, 96% ee

2.8f
64% Yield
11:1 dr, 90% ee

2.8g
76% Yield
18:1 dr, 96% ee

2.8h
71% Yield
19:1 dr, 95% ee

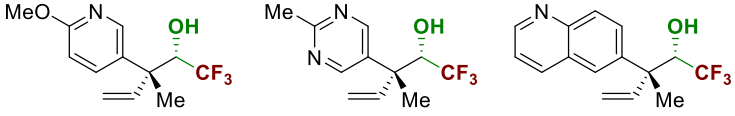


2.8i
58% Yield
13:1 dr, 96% ee

2.8j
74% Yield
>20:1 dr, 96% ee

2.8k
86% Yield
20:1 dr, 96% ee

2.8l
68% Yield
13:1 dr, 94% ee[b]



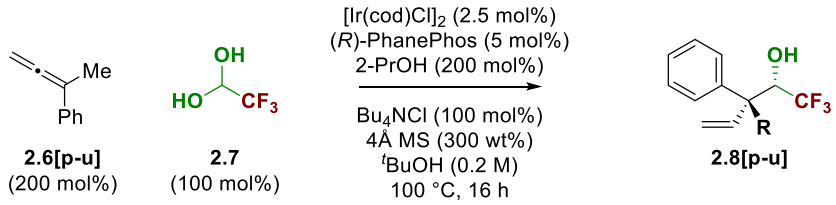
2.8m
68% Yield
19:1 dr, 97% ee

2.8n
69% Yield
15:1 dr, 96% ee

2.8o
70% Yield
>20:1 dr, 95% ee

[a]Diastereoselectivities were determined by ^{19}F NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary-phase HPLC analysis. Yield reported are for material isolated by silica gel chromatography. [b]8h.

Table 2.4 Iridium-Catalyzed Coupling of Allenes **2.6[p-u]** with Fluoral Hydrate **2.7** To Form Adducts **2.8[p-u]** Bearing Acyclic Quaternary Carbon Stereocenters[a]

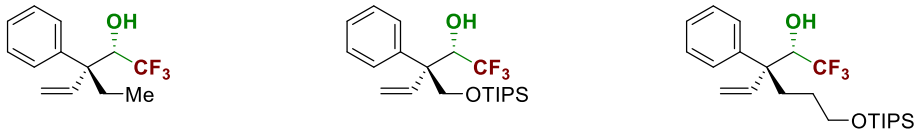


2.6[p-u] (200 mol%) | **2.7** (100 mol%) | **2.8[p-u]**

2.6p, R = Et
2.6s, R = $(CH_2)_3$NPhth

2.6q, R = CH_2OTIPS
2.6t, R = $(CH_2)_2$4-F-Ph

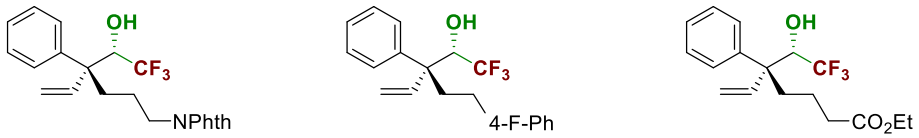
2.6r, R = $(CH_2)_3$OTIPS
2.6u, R = $(CH_2)_3CO_2Et$



2.8p
76% Yield
12:1 dr, 93% ee

2.8q
58% Yield
20:1 dr, 99% ee

2.8r
84% Yield
10:1 dr, 95% ee



2.8s
81% Yield
15:1 dr, 93% ee

2.8t
72% Yield
11:1 dr, 96% ee

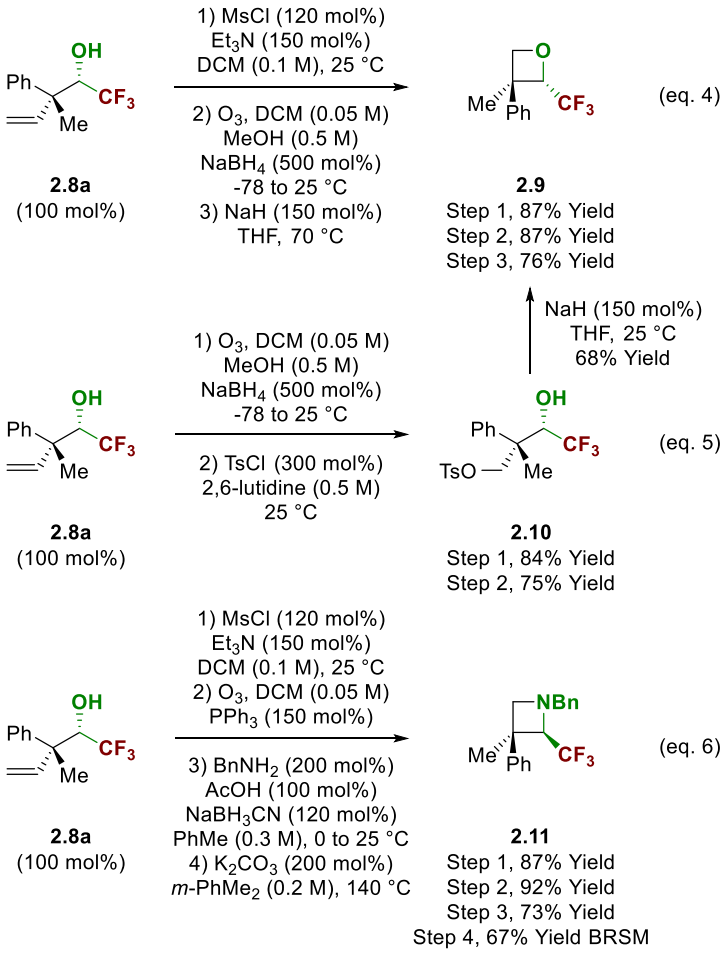
2.8u
65% Yield
9:1 dr, 96% ee

[a]Diastereoselectivities were determined by ^{19}F NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary-phase HPLC analysis. Yield reported are for material isolated by silica gel chromatography.

To briefly illustrate the utility of the reaction products, fluoral adduct **2.8a** was converted to the CF_3-oxetane **2.9a**, which bears a quaternary carbon stereocenter (Scheme 2.4, eq. 4).[3d] Oxetanes have emerged as useful building blocks in medicinal chemistry due to their ability to serve as carbonyl and gem-dimethyl isosteres.[31] Recently, CF_3-oxetanes were shown to function as more polar *tert*-butyl isosteres.[32] To prepare CF_3-oxetane **2.9**, fluoral adduct **2.8a** was transformed to the mesylate and subjected to ozonolysis conditions. The resulting primary alcohol was exposed to sodium hydride to provide oxetane **2.9** (Scheme 2.4, eq. 4). As corroborated by the conversion of primary tosylate **2.10** to oxetane **2.9** (Scheme 2.4, eq. 5), the formation of **2.9** proceeds via secondary to primary methanesulfonate transfer. Just as trifluoroethylamines serve as amide bioisosteres,[33] CF_3-

azetidines[34] may be viewed as β-lactam mimics. To prepare CF_3-azetidine **2.11**, fluoral adduct **2.8a** was converted the mesylate and subjected to ozonation conditions to deliver the corresponding aldehyde. Reductive amination−cyclization provided CF_3-azetidine **2.11** (Scheme 2.4, eq. 6).

Scheme 2.4 Preparation of CF_3-oxetanes and CF_3-azetidines from Adduct **2.8a**



2.3.3 Mechanism and Discussion

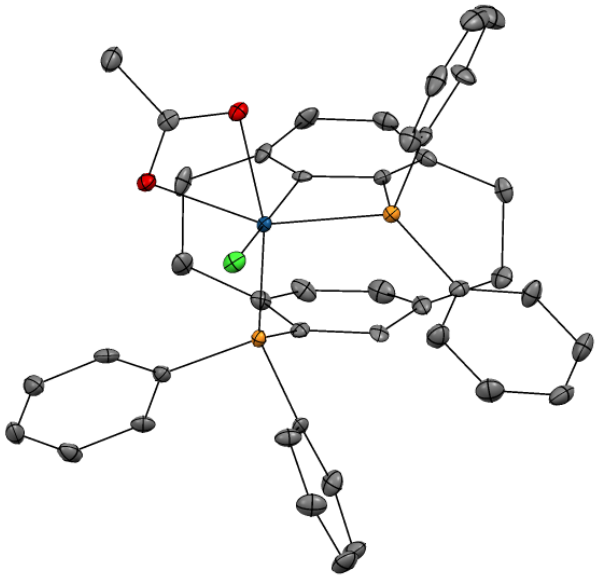
Insight into the unusual effectiveness of the iridium–PhanePhos catalyst was essential in terms of formulating an accurate interpretation of the catalytic mechanism. Products of allene–fluoral reductive coupling were not formed upon use of other chelating

phosphine ligands such as BINAP or SEGPHOS under otherwise identical conditions. The same is true for previously reported iridium–PhanePhos-catalyzed couplings of methanol with 1,3-dienes[3c] and CF_3-allenes.[22] Consequently, the fact that cyclometalated π-allyliridium C,O-benzoate complexes (Figure 2.1)[27c] promote C–C coupling in the aforesaid processes (albeit with suboptimal levels of stereocontrol) was deemed significant. This observation raised the question of whether the unique topology of PhanePhos rendered this ligand susceptible to cyclometalation. Although cyclometalated complexes of PhanePhos have not been reported, a relatively short contact of 3.56 Å is found in the X-ray crystal structure of a palladium–PhanePhos complex[35] between metal and the *ortho*-carbon atom of the cyclophane ring. For an iridium center, which has a larger atomic radius, one could easily imagine an agostic interaction or C–H oxidative addition to form a cyclometalated complex. With these thoughts in mind, an effort was made to prepare a cyclometalated iridium–PhanePhos complex and evaluate its catalytic activity.

In the event, heating a THF solution of $[Ir(cod)Cl]_2$ (100 mol%), (*R*)-PhanePhos (200 mol%) and allyl acetate (400 mol%) at 100 °C for 1 h gave a yellow residue, which upon flash silica gel column chromatography delivered the 4-membered metallacycle Ir-PP-**I** in up to 60% yield. The structural assignment of Ir-PP-**I** was corroborated by single-crystal X-ray diffraction analysis (Figure 2.3). The cyclometalated iridium complex is of distorted octahedral geometry, with the two phosphorus atoms of PhanePhos and acetate lying in the same plane and with the chloride and aryl moieties apical to the plane. The distance between the phosphorus atoms (3.34 Å) is noticeably less than that found in the related square planar Pd(*rac*-PhanePhos)Cl_2 complex (3.62 Å).[35] Additionally, the P–Ir–P "bite angle" (95.90°) is significantly compressed compared to that found in the palladium complex (103.69°).[35] The P–Ir–C bond angle of the iridacycle is 67.95°, with an Ir–C bond length of 2.04 Å. The bond length of the cyclometalated Ir–P is 2.24 Å, which is slightly

shorter than the other Ir–P bond, which has a bond length of 2.26 Å. The differential trans influence of these two phosphorus atoms is reflected by the disparity between the two Ir–O bond lengths of the acetate moiety. The Ir–O bond that is trans to the activated phosphorus atom has a bond length of 2.19 Å, which is slightly longer than the Ir–O bond trans to the non-cyclometalated phosphorus atom, which has a bond length of 2.15 Å.

Figure 2.3 Structure of the Cyclometalated Iridium–(*R*)-PhanePhos Complex Ir-PP-**I** As Determined by Single-Crystal X-Ray Diffraction.

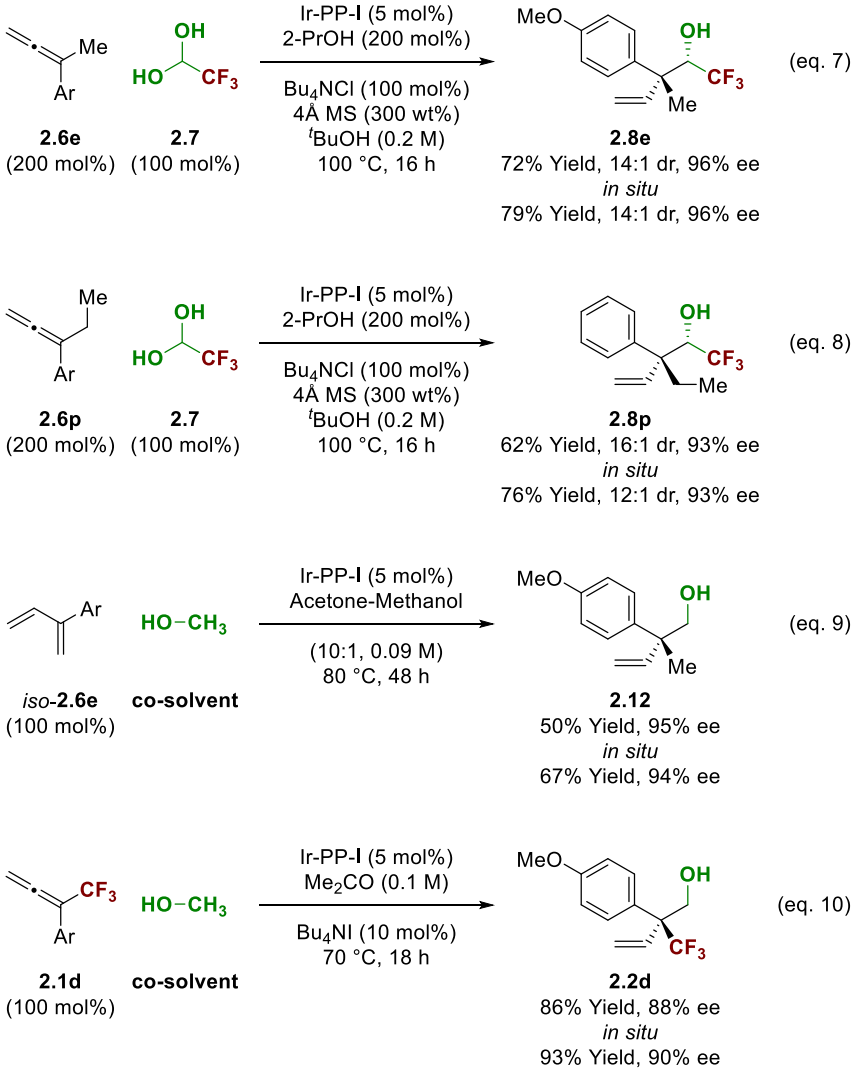


Displacement ellipsoids are scaled to the 50% probability level.

To probe the catalytic competency of the cyclometalated complex, allene **2.6e** was exposed to fluoral hydrate **2.7** in the presence of Ir-PP-**I** (5 mol%) under otherwise standard conditions. The product of reductive coupling **2.8e** was formed in 72% yield in a 14:1 diastereomeric ratio and 96% enantiomeric excess (Figure 2.4, eq. 7). Similarly, allene **2.6p** was exposed to fluoral hydrate **2.7** in the presence of Ir-PP-**I** (5 mol%) under otherwise standard conditions to furnish the reductive coupling product **2.8p** in 62% yield in a 16:1 diastereomeric ratio and 93% enantiomeric excess (Figure 2.4, eq. 8). These data are in

good alignment with the yields and stereoselectivities observed in reactions in which the catalyst is generated in situ from $[Ir(cod)Cl]_2$ (2.5 mol%) and (*R*)-PhanePhos (5 mol%) (Tables 2.3 and 2.4, respectively). The cyclometalated complex Ir-PP-**I** is also a competent catalyst in the previously reported iridium–PhanePhos-catalyzed couplings of methanol

Figure 2.4 Corroboration of Catalytic Competency of Ir-PP-**I** for All Iridium–(*R*)-PhanePhos-Catalyzed Transfer Hydrogenative Carbonyl Additions[a]

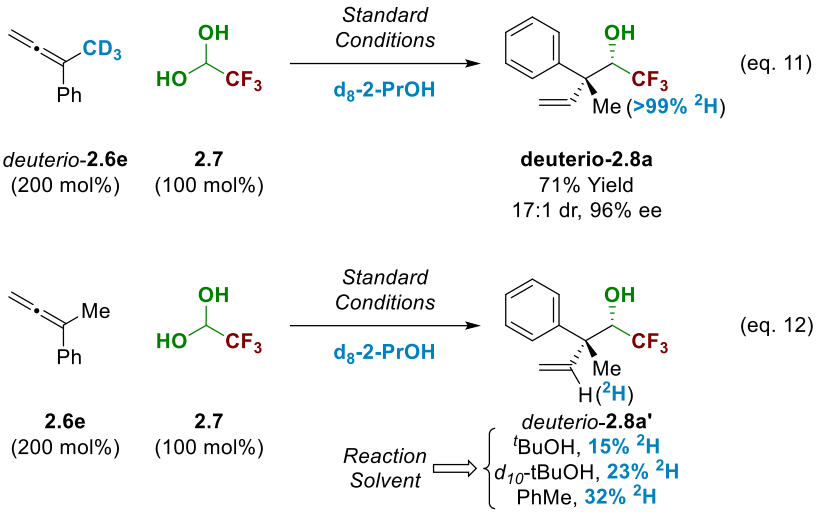


[a]Diastereoselectivities were determined by NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chrial stationary phase HPLC analysis. Yields reported are for material isolated by silica gel chromatography.

with 1,3-dienes (Figure 2.4, eq. 9)[3c] and CF_3-allenes (Figure 2.4, eq. 10).[22] These data (eqs 7–10) corroborate intervention of a cyclometalated catalyst related to Ir-PP-**I** in the present allene–fluoral reductive coupling and the previously reported transfer hydrogenative C–C couplings of dienes[3c] or CF_3-allenes.[22] While roughly equivalent stereoselectivities are observed using the preformed complex Ir-PP-**I**, slightly lower yields are evident. This may be due to the fact that the catalyst generated in situ incorporates a monodentate chloride counterion, whereas Ir-PP-**I** contains a bidentate acetate counterion, which may inhibit catalysis.

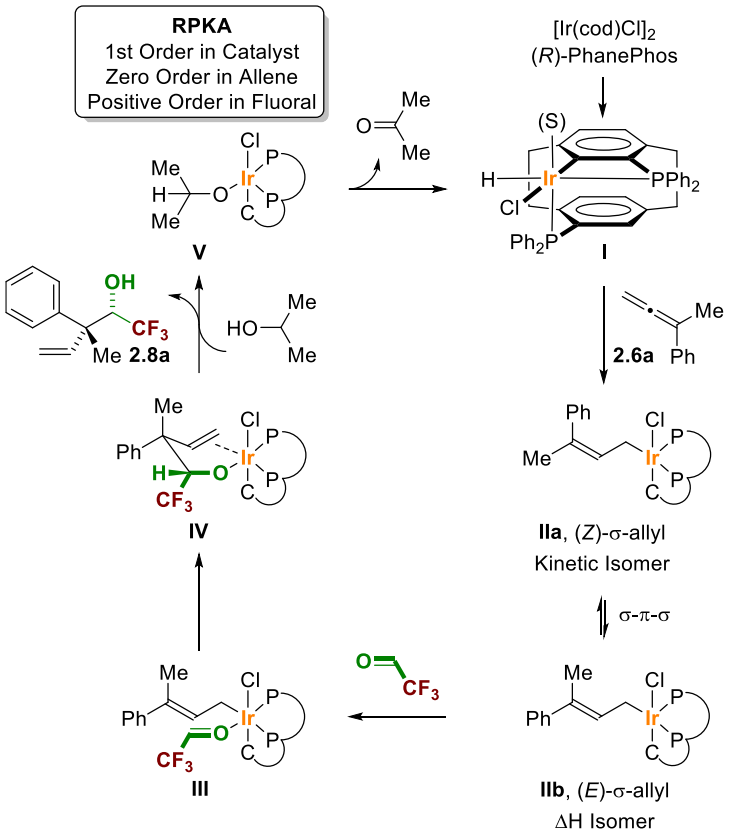
To gain further insight into the catalytic mechanism, a series of deuterium labeling experiments were conducted (eqs 11 and 12). Exposure of fluoral hydrate **2.7** to *deuterio*-**2.6a**, which incorporates a fully deuterated methyl group, under standard reaction conditions delivers *deuterio*-**2.8a** (Scheme 2.5, eq. 11). Deuterium is completely retained at the methyl group and is not redistributed to any other position. This experiment demonstrates that the reaction does not proceed by way of allene-to-diene isomerization. Indeed, the isomeric diene was prepared and subjected to standard reaction conditions and was not a competent partner for C–C coupling. The coupling of **2.6a** and **2.7** mediated by d_8-2-propanol under otherwise standard conditions delivers *deuterio*-**2.8a′** (Scheme 2.5, eq. 12). Deuterium is incorporated exclusively at the interior vinylic position (15% ^{2}H). Exchange between iridium hydrides and the deuterium atoms of D_2O is well-documented,[36] and incomplete deuterium incorporation is likely due to H–D exchange with *tert*-butanol or water associated with aqueous fluoral hydrate. Consistent with this hypothesis, when the reaction is conducted in d_{10}-*tert*-butanol or toluene, enhanced levels of deuterium incorporation are observed (Scheme 2.5, eq. 12).

Scheme 2.5 Deuterium Labeling Studies



The collective data are consistent with the indicated catalytic mechanism (Scheme 2.6). Entry into the catalytic cycle is achieved via C–H oxidative addition of the *ortho*-C–H bond of PhanePhos to iridium(I). Allene hydrometalation from the resulting iridium(III) hydride **I** delivers the kinetic (*Z*)-σ-allyliridium isomer **IIa**. Isomerization to the thermodynamically preferred (*E*)-σ-allyliridium isomer **IIb** is followed by association of fluoral and carbonyl addition to furnish the homoallylic iridium(III) alkoxide **IV**. Alkoxide exchange with 2-propanol releases the product of carbonyl addition **2.8a**. β-Hydride elimination from the 2-propoxyiridium(III) species **V** regenerates the iridium(III) hydride **I** to close the catalytic cycle. Knowing that the active catalyst is a cyclometalated halide-containing iridium(III) complex, one can better understand how halides "tune" the environment at the iridium center to influence reactivity and selectivity. In the present transformation, the additive Bu_4NCl may assist by preserving chloride at the iridium(III) center, while in previously discussed couplings of methanol with CF_3-allenes,[22] Bu_4NI likely substitutes the chloride at iridium(III).

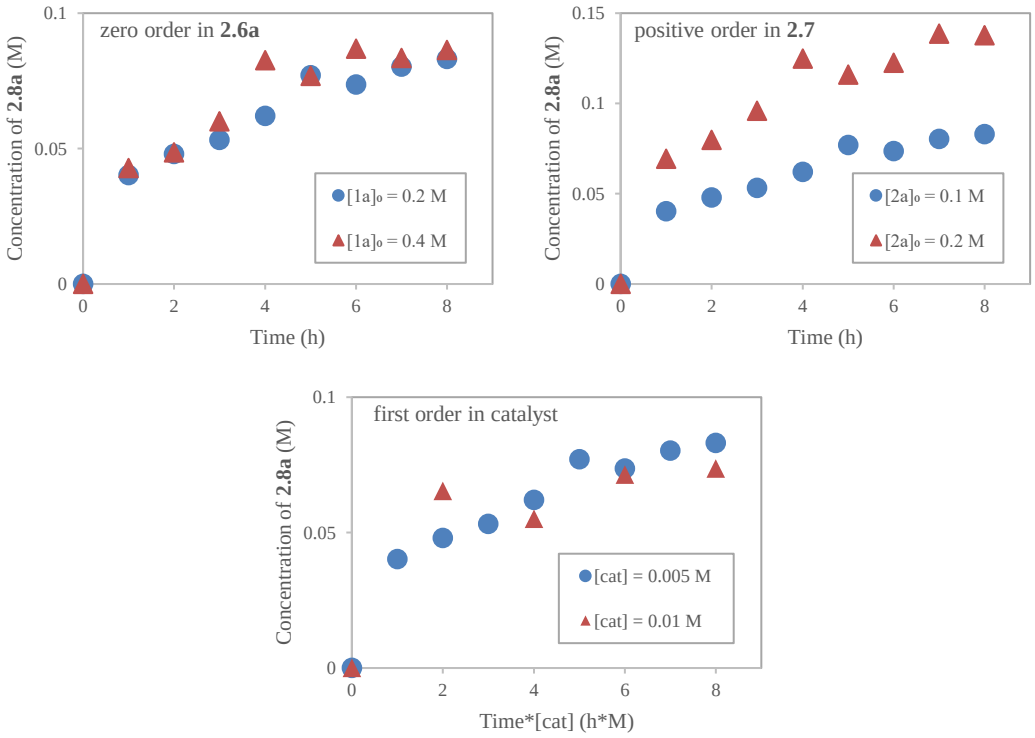
Scheme 2.6 Proposed Catalytic Mechanism for Iridium–PhanePhos-Catalyzed Allene–Fluoral Reductive Coupling Mediated by 2-Propanol



To gain further mechanistic insight, reaction progress kinetic analysis (RPKA) was applied to the coupling of allene **2.6a** with fluoral hydrate **2.7** to form adduct **2.8a**.[37,38] Due to the volatile nature of the reactants and the complex equilibria between fluoral, fluoral hydrate, and hemiacetals that arise upon addition of 2-propanol and *tert*-butanol, the progress of a single reaction could not be monitored. Therefore, a series of reactions were conducted in parallel: for each successive time point, an individual reaction was stopped and the extent of product formation was determined by GC analysis using an internal standard. As each data point derives from a separate experiment, the quality of the data was not ideal; nevertheless, several significant conclusions could be drawn.

The results of experiments carried out using the "different excess" protocol elucidate the order in allene **2.6a** and fluoral hydrate **2.7** (Figure 2.5). The observed overlap between data sets indicates zero-order kinetics in allene, since the rate of product formation is not affected by the change of initial concentration of allene (Figure 2.5, left). In contrast, higher concentrations of **2.6a** result in faster rates of product formation, which suggests a positive order in fluoral (Figure 2.5, right). Evaluation of the effect of increasing catalyst

Figure 2.5 Reaction Progress Kinetic Analysis of the Reductive Coupling of Allene **2.6a** and Fluoral **2.7**

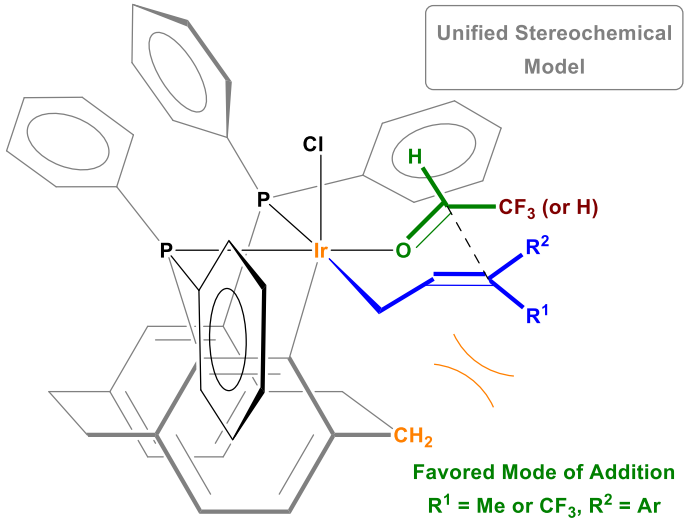


Product formation as monitored by GC analysis in reactions carried out utilizing "different excess" protocol: [cat] = 0.005 M; [TBAC] = 0.1 M; [2-propanol] = 0.2 M; (a) [**2.7**]$_0$ = 0.1 M, [**2.6a**]$_0$ = as noted; (b) [**2.6a**]$_0$ = 0.2 M, [**2.7**]$_0$ = as noted. (c) Time adjustment of product formation in varying catalyst loading reactions as monitored by GC analysis: [**2.6a**] = 0.2 M; [**2.7**] = 0.1 M; [TBAC] = 0.1 M; [2-propanol] = 0.2 M; [cat] = as noted.

loading using Burés's method[39] suggests the reaction is first order in catalyst (Figure 2.5, bottom). Furthermore, results of a set of experiments performed using the "same excess" protocol indicate minimal catalyst deactivation occurs (see Experimental Data). These data corroborate a catalytic mechanism involving rapid allene hydrometalation followed by turnover-limiting carbonyl addition (Scheme 2.6). These data also implicate the π-allyliridium species, which could be detected via high-resolution mass spectrometry as the catalyst resting state.

Initial computational studies, performed by colleagues at King Abdullah University of Science and Technology (KAUST), were aimed at formulating a unified stereochemical model accounting for relative and absolute stereochemistry in the present and prior[3c,22] iridium–(*R*)-PhanePhos-catalyzed transfer hydrogenative carbonyl additions (Figure 4, eqs 7−10). Accordingly, 48 different conformations based on a Zimmerman–Traxler-type transition structure[40] were thus computationally analyzed[41] to identify the transition state with the lowest energy barrier. In the most favored transition state (Figure 2.6), the σ-allyl occupies a coordination site that minimizes steric repulsion with the CH_2 moiety of the cyclophane ethano linkage that resides *ortho* to iridium. At the same time, nonbonded interactions between the terminal aryl moiety of the σ-allyl and the cyclometalated phenyl ring are decreased. The carbonyl electrophile, fluoral, can then enter the coordination site *trans* to the PPh_2 moiety of the iridacycle and *syn* to Ir–Cl with the CF_3 pointing away from the iridium center. The orientation of the fluoral C–H bond suggests possible intervention of a formyl C–H bond with the chloride ligand.[42] Addition of the σ-allyl to the *Si*-face of the carbonyl through a closed transition structure defines enantiotopic π-facial selectivity. This model is also applicable to iridium– (*R*)-PhanePhos-catalyzed couplings of methanol with 1,3-dienes[3c] and the above described CF_3-allenes.[22]

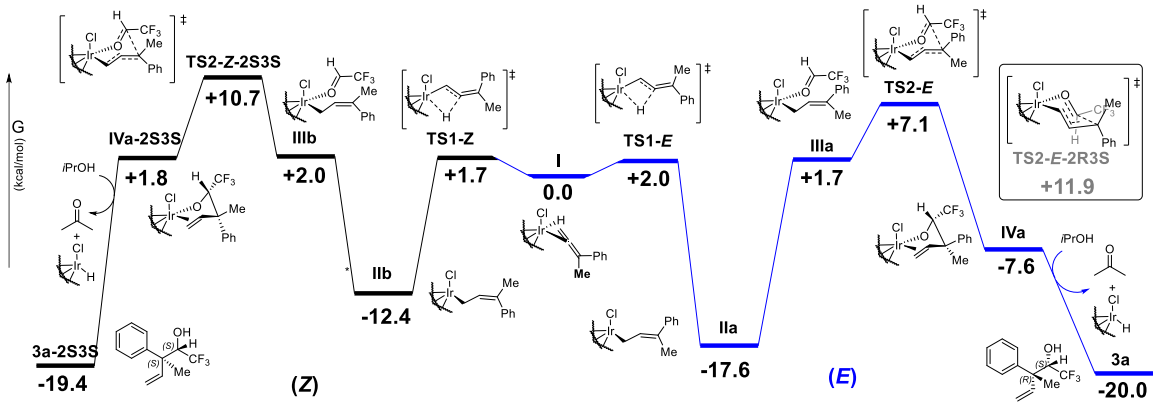
Figure 2.6 Computationally Determined Stereochemical Model Accounting for Relative and Absolute Stereochemistry for All Iridium–(*R*)-PhanePhos-Catalyzed Transfer Hydrogenative Carbonyl Additions



Computational studies were used to further assess the veracity of our interpretation of the catalytic mechanism (Scheme 2.6). Allene hydrometalation from intermediate **I**, an iridium(III) hydride−allene complex, delivers the kinetic (*Z*)- σ-allyliridium isomer **IIb**, which can interconvert with the thermodynamically preferred (*E*)-σ-allyliridium isomer **IIa**. The Curtin−Hammett situation[29] favors the reaction to proceed by association of fluoral to **IIIa** followed by carbonyl addition via **TS2-*E*** to furnish the homoallylic iridium(III) alkoxide **IVa**. Alkoxide exchange with 2-propanol releases the product of carbonyl addition **2.8a** and regenerates the iridium-(III) hydride coordinated with an allene after β-hydride elimination to close the catalytic cycle. Consistent with the excellent levels of diastereo- and enantioselectivity that are observed, the transition state leading to the disfavored enantiomer, **TS2-*E*-2R3S**, requires the fluoral carbonyl group to become anti-periplanar to the Ir–Cl bond, which results in a higher energy barrier due to the increased steric interactions with the cyclometalated phenyl ring and the *ortho*-CH_2 group of the PhanePhos ligand. Within the same core geometry at iridium, the second lowest transition

state, **TS2-*Z*-2S3S**, will afford a diastereomer from the (*Z*)-isomer **IIb** with the same stereoselectivity for the allylation of fluoral. Notably, both computational studies and RPKA implicate rapid allene hydrometalation followed by turnover-limiting carbonyl addition with the allyliridium species as a potential catalyst resting state.

Scheme 2.7 Computationally Determined Energy Profiles of the Proposed Catalytic Mechanism



2.3.4 Conclusion

In summary, a highly regio- and enantioselective iridium-catalyzed allene−fluoral reductive coupling mediated by 2-propanol was achieved. This method enables generation of enantiomerically enriched quaternary carbon stereocenters in the context of a CF_3-bearing stereodiad. Of greater significance, a chromatographically stable cyclometalated iridium–(*R*)-PhanePhos complex, Ir-PP-**I**, was identified that is catalytically competent in the present allene–fluoral reductive couplings as well as previously reported iridium−PhanePhos-catalyzed C–C couplings of methanol with dienes[3c] or CF_3-allenes.[22] These findings suggest that cyclometalated iridium–PhanePhos complexes akin to Ir-PP-**I** may constitute a privileged catalyst class. A catalytic mechanism involving rapid allene hydrometallation followed by turnover-limiting carbonyl addition was corroborated by deuterium labeling studies, reaction progress kinetic analysis (RPKA) and DFT

calculations. Computational studies also were used to formulate a unified stereochemical model that accounts for the origins of enantioselectivity in the present fluoral–allene reductive couplings and previously reported iridium–PhanePhos-catalyzed C–C couplings of methanol with dienes[3c] or CF_3-allenes.[22]

2.4 Summary and Outlook

In conclusion, it has been demonstrated that iridium complexes modified by PhanePhos catalyze the methanol-mediated hydrohydroxymethylation of CF_3-allenes and the 2-propanol-mediated allene–fluoral reductive coupling with high levels of regio- and enantioselectivities. The identification of the cyclometalated iridium–(*R*)-PhanePhos complex, Ir-PP-**I**, was significant and allowed for greater understanding of catalyst topology. Further exploitation of this catalyst system will likely focus on the discovery and development of expanded allylative alcohol-mediated carbonyl addition reactions.

2.5 EXPERIMENTAL DETAILS

2.5.1 General Information

All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. Acetone (HPLC grade), absolute methanol and ethanol were used as received from vendors (Fischer and Sigma Aldrich) without further purification. [Ir(cod)Cl]2, Ir(cod)(acac) and (R)-PhanePhos ligand were used as received from Strem Chemicals Inc. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[43] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in CAM, *p*-Anisaldehyde (PAA), or KMnO4 stain solution followed by heating. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}. 4Å molecular sieves (Sigma Aldrich, powder, 325 mesh particle size) were dried prior to each use by heating with a propane torch *in vacuo* and cooling to room temperature under Ar. Trifluoromethylallenes **2.1a**, **2.1d**, **2.1h**, **2.1i** and **2.1o** were prepared according to literature procedure and compared to authentic samples.[44,45] Trifluoromethylallenes 1b,1c, 1e-1g, 1j-1n were prepared were prepared in an analogous manner. NaO_2CCBrF_2 was prepared according to literature procedures.[46] 1,1-Disubstituted allenes **2.6[a–e]**[47], **2.6g**[48], **2.6h**[48], **2.6i**[48], **2.6p**[47], **2.6q**[49], **2.6s**,[49] and **2.6u**[50] were prepared according to literature procedures. 1,1-Disubstituted allenes were stable for several months at -20 °C, but some

degradation can be observed at higher temperatures. Racemic reactions were conducted using a 1:1 ratio of (*R*)- and (*S*)-PhanePhos.

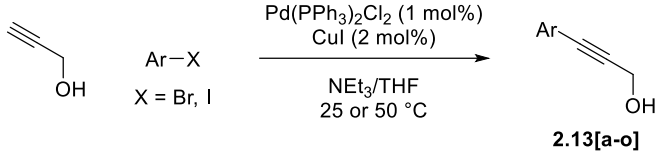
2.5.2 Spectroscopy and Spectrometry

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian INOVA (500 MHz) spectrometer equipped with a Bruker AVANCE III cryoprobe. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian INOVA (125 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian INOVA (470 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00s).

2.5.3 Experimental Data for Section 2.2

2.5.3.1 General Procedures

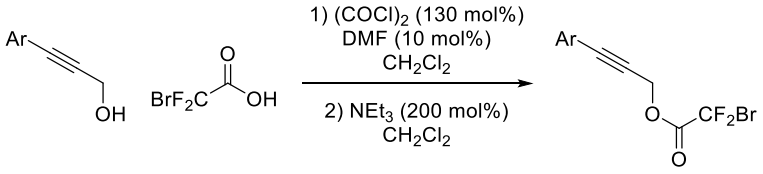
General Procedure A



2.13[a-o]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with $Pd(PPh_3)_2Cl_2$ (1 mol%) and CuI (2 mol%) was added THF (1 M) followed by Et_3N (1 M). The reaction mixture was allowed to stir for five minutes at 0 °C. Aryl iodide (100 mol%) was added followed by propargyl alcohol (110 mol%) and the reaction mixture was allowed to stir at room temperature for 16 hours. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the propagylic alcohols. For aryl bromides, the reaction mixture was allowed to stir at 50 °C for 16 hours.[45]

General Procedure B

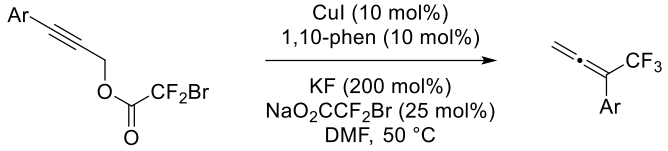


2.14[a-o]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with bromodifluoroacetic acid (140 mol%) in CH_2Cl_2 (0.4 M) was added dimethylformamide (10 mol%) followed by oxalyl chloride (130 mol%). The reaction mixture was allowed to stir for 1 hour at room temperature, at which point the reaction mixture was added dropwise via syringe to a cooled (0 °C) solution of propargyl alcohol (100 mol%) and Et_3N (200 mol%) in CH_2Cl_2 (0.4 M). The reaction mixture was allowed

to stir for 14 hours at room temperature. To the reaction mixture was added HCl (1 N). The reaction mixture was transferred to a separatory funnel. The organic layer was washed with H_2O (2x) and the combined aqueous layers were extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the propargyl bromodifluoroacetates. [Note: some propargyl bromodifluoroacetates are prone to hydrolysis on silica gel so a minimum amount of silica gel was used].[45]

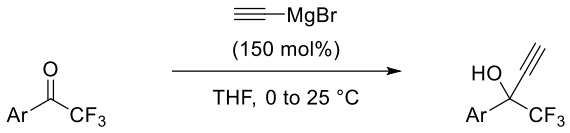
General Procedure C



2.1[a-o]

To a dried pressure tube charged with KF (200 mol%), CuI (10 mol%), 1,10-phenanthroline (10 mol%), and NaO_2CCF_2Br (25 mol%) was added propargyl bromodifluoroacetate (100 mol%) followed by DMF (1 M). The reaction mixture was flushed with Ar, sealed and allowed to stir at 50 °C for 14 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc. The reaction mixture was transferred to a separatory funnel. The organic layer was washed with H_2O (2x), brine, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the trifluoromethylallenes.[45]

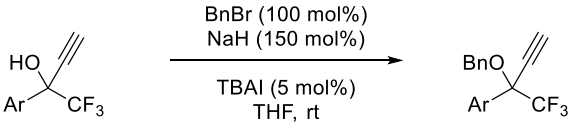
General Procedure D



2.15[a-o]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with aryl trifluoromethyl ketone (100 mol%) in THF (0.5 M) at 0 °C was added ethynyl magnesium bromide (0.5 M solution in THF, 150 mol%). The reaction mixture was allowed to stir at room temperature until complete consumption of starting material was observed (TLC, 1-2 hours). To the reaction mixture was added saturated NH_4Cl (aq). The reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the tertiary propargylic alcohols.[44]

General Procedure E

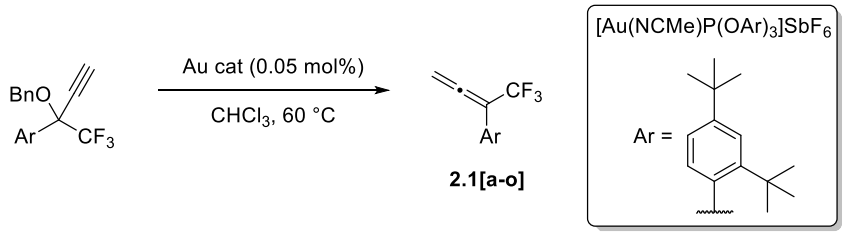


2.16[a-o]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charge with tertiary propargylic alcohol (100 mol%) in THF (0.5 M) at 0 °C was added NaH (150 mol%, 60% w/w) and the reaction mixture was allowed to stir for 30 minutes. Benzyl bromide (100 mol%) and TBAI (5 mol%) were added and the reaction mixture was allowed to stir for 14 hours at room temperature. Saturated NH_4Cl (aq) and Et_2O were added to the reaction mixture and the reaction mixture was transferred to a separatory

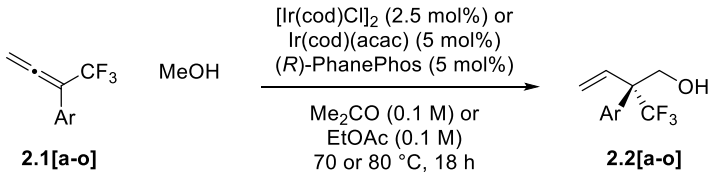
funnel. The organic layer was washed with H_2O, brine, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was subjected to flash chromatography (SiO_2) under the conditions noted to afford the benzyl protected propargylic alcohol. [Note: it is essential that any trace of unreacted benzyl bromide be removed during the purification as this can interfere with the following reactions].[44]

General Procedure F



To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with benzyl protected propargylic alcohol (100 mol%) in $CHCl_3$ (0.2 M) was added gold catalyst (see above inset, 0.05 mol%) and the reaction mixture was allowed to stir at 60 °C for 1.5 hours. The solvent was removed in vacuo. The residue was subjected to flash column chromatography under the conditions noted to afford the trifluoromethylallenes.[44]

General Procedure G

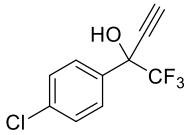


To a dried pressure tube under an argon atmosphere charged with iridium precatalyst (5 mol% Ir), (*R*)-PhanePhos (5 mol%) was added solvent (EtOAc or Me_2CO) (0.1 M)

followed by MeOH (1 M) and trifluoromethylallene (100 mol%). The reaction mixture was allowed to stir for 18 hours at 70 °C (for Me_2CO) or 80 °C (for EtOAc). The solvent was removed in vacuo and residue was subjected to flash column chromatography (SiO_2) under the noted conditions to furnish the product of hydrohydroxymethylation.

2.5.3.2 Procedures and Spectral Data for the Synthesis of Trifluoromethylallenes 2.1[b, c, e–g, j–n]

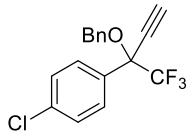
2-(4-chlorophenyl)-1,1,1-trifluorobut-3-yn-2-ol (2.15b)



2.15b

4’-chloro-2,2,2-trifluoroacetophenone (1.67 g, 8 mmol) was subjected to general procedure D to furnish the title compound 8b, which was used in the next step without purification.

1-(2-(benzyloxy)-1,1,1-trifluorobut-3-yn-2-yl)-4-chlorobenzene (2.16b)



2.16b

Crude tertiary propargylic alcohol 2.15b was subjected to general procedure E. Upon flash column chromatography (SiO_2, 2:98 to 1:5 Et_2O/hexanes), the title compound 2.16b (1.12 g, 3.4 mmol) was obtained as a light yellow oil in 43% yield over two steps.

R_f = 0.35 (1:5 Et_2O/hexanes).

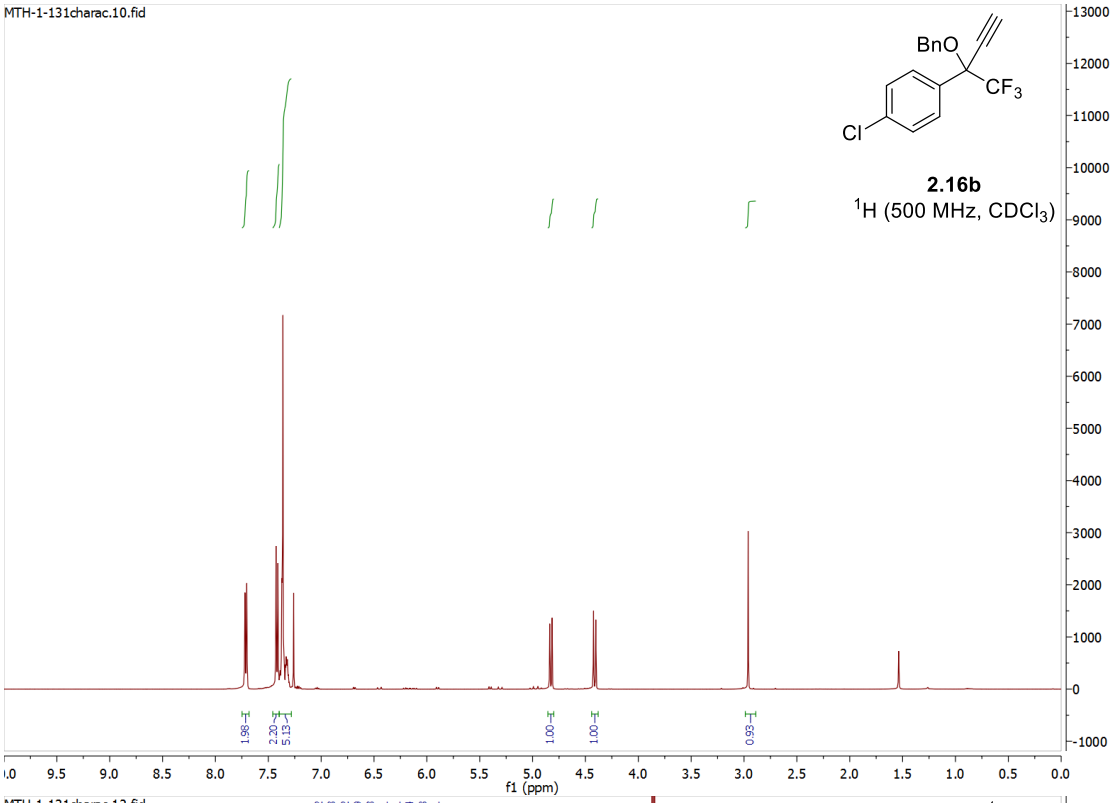
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.39-7.30 (m, 5H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 2.96 (s, 1H).

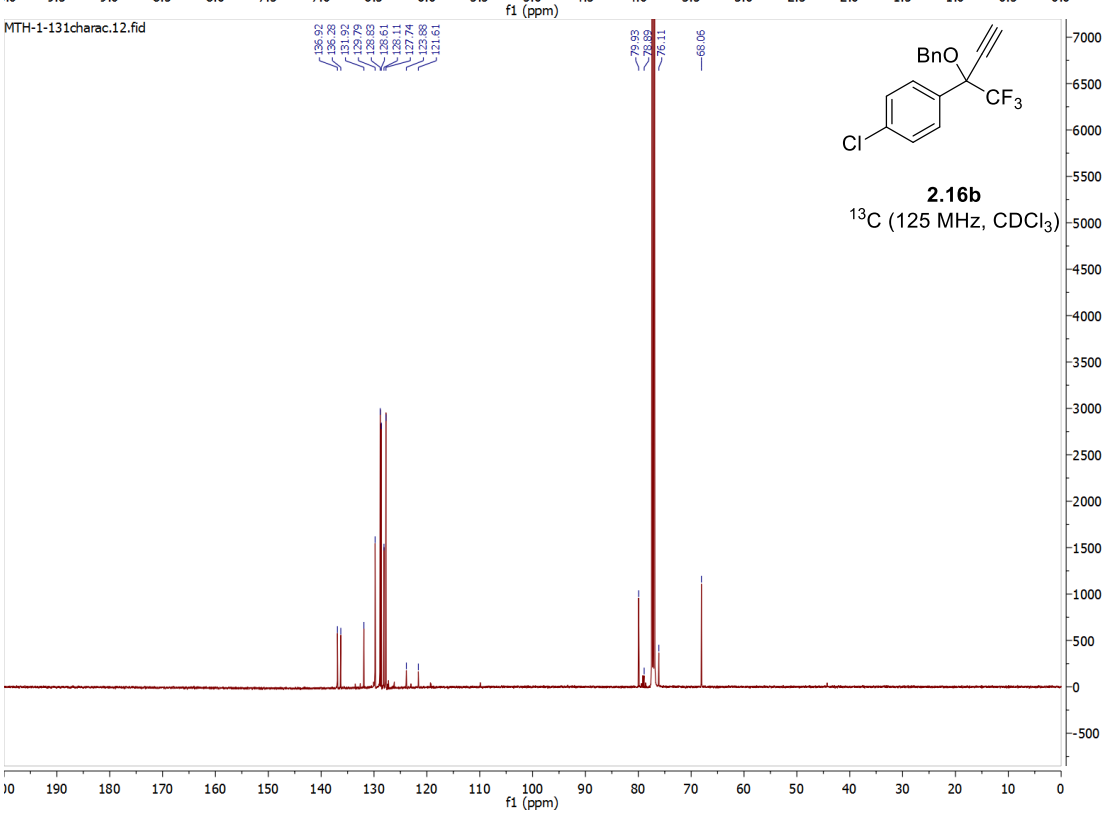
^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.9, 136.3, 131.9, 129.8, 128.8, 128.6, 128.1, 127.7, 122.8 (q, *J* = 279 Hz), 80.0, 79.0 (q, *J* = 31 Hz), 76.1, 68.1.

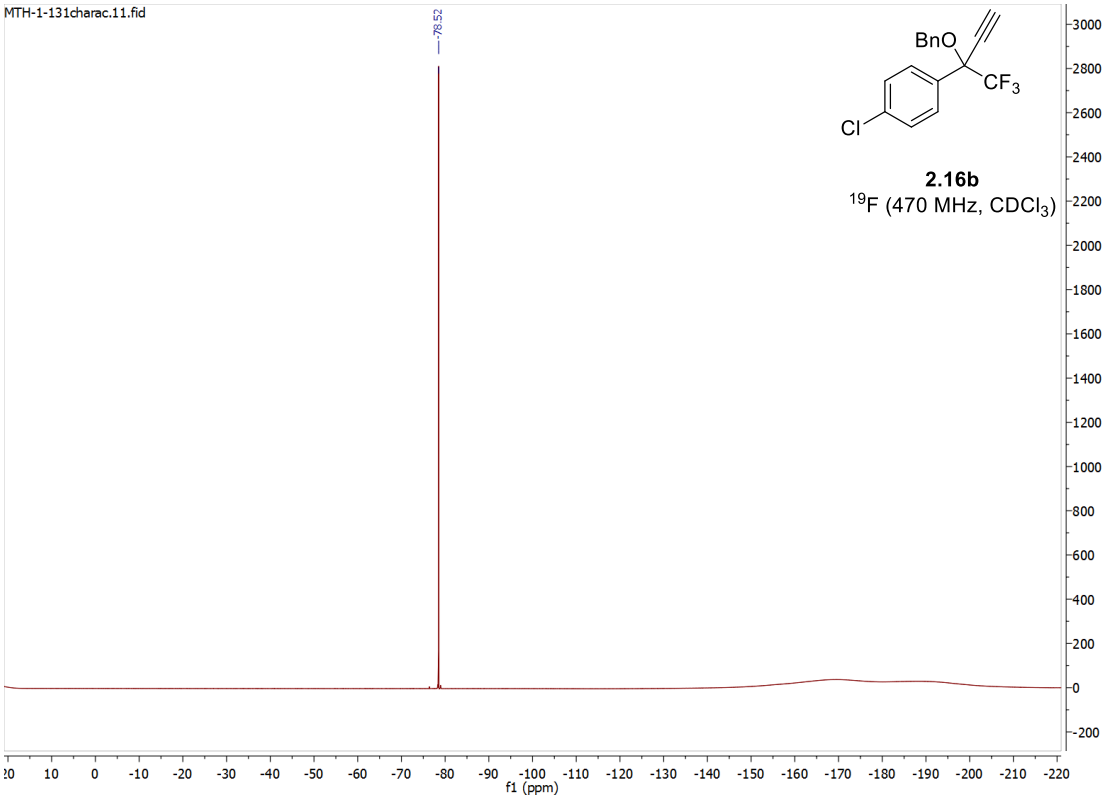
^{19}F NMR (470 MHz, $CDCl_3$) δ: -78.5.

HRMS (CI+, *m/z*) for $C_{17}H_{12}OF_3Cl$: calcd. = 324.0529; found = 324.0530.

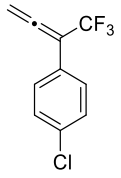
FTIR (neat): 3299, 3036, 2970, 2121, 1595, 1489, 1382, 1185, 1175, 1093, 1-61, 1017, 978, 825 cm^{-1}.


MTH-1-131charac.10.fid
BnO
CF3
Cl
2.16b
1H (500 MHz, CDCl3)
1.98
2.20
5.13
1.00
1.00
0.93
f1 (ppm)


MTH-1-131charac.12.fid
136.92
136.28
131.92
129.79
128.83
128.61
128.11
127.74
123.88
121.61
79.93
78.89
76.11
68.06
BnO
CF3
Cl
2.16b
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-1-131charac.11.fid
-78.52
BnO
CF3
Cl
2.16b
19F (470 MHz, CDCl3)
f1 (ppm)

1-bromo-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (2.1b)

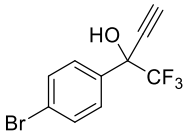


2.1b

Benzyl protected propargylic alcohol 9b (300 mg, 0.93 mmol) was subjected to general procedure F. Upon flash column chromatography (SiO_2, pentane) title compound 1b (150 mg, 0.69 mmol) was obtained as a colourless oil in 74% yield.

The spectral data recorded for this compound was in complete agreement with the literature.[51]

2-(4-bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol (2.15c)



2.15c

4'-bromo-2,2,2-trifluoroacetophenone (2.53 g, 10 mmol) was subjected to general procedure D. Upon flash column chromatography (SiO2, 1:5 Et2O/hexanes), the title compound 8c (1.98 g, 7.1 mmol) was obtained as a light yellow oil in 71% yield.

Rf = 0.25 (1:5 Et2O/hexanes).

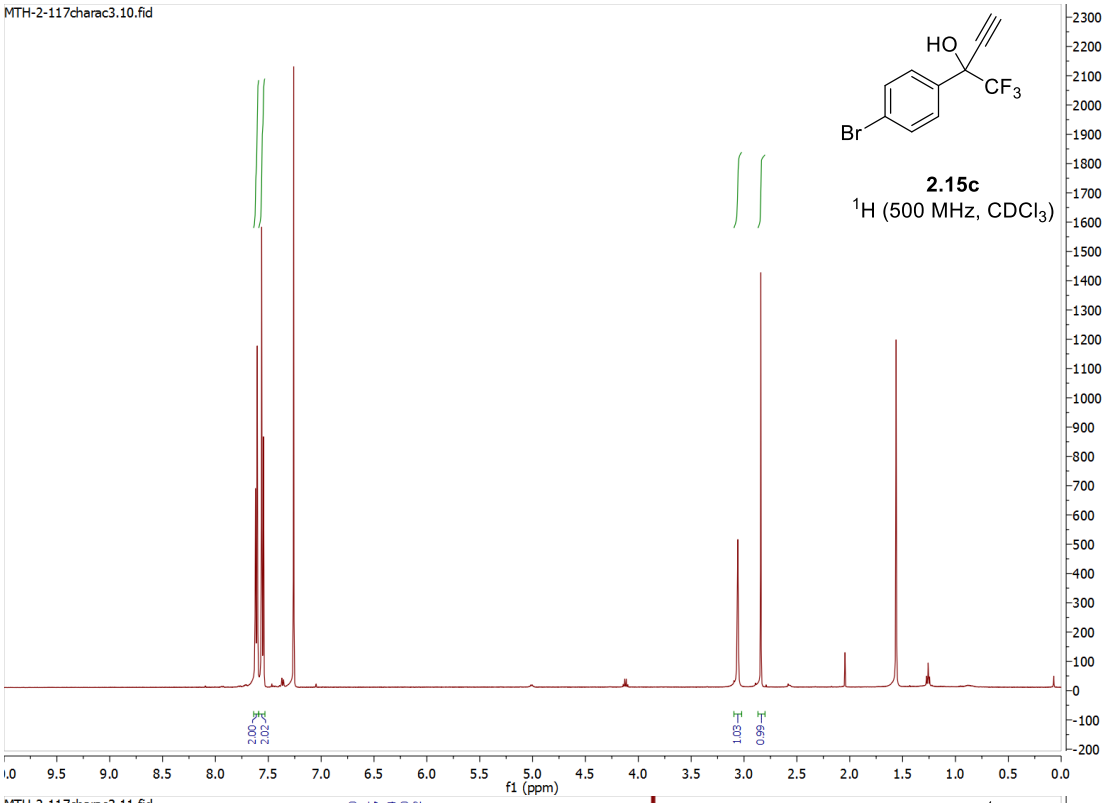
^{1}H NMR (500 MHz, CDCl3) δ: 7.61 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 3.06 (br s, 1H), 2.84 (s, 1H).

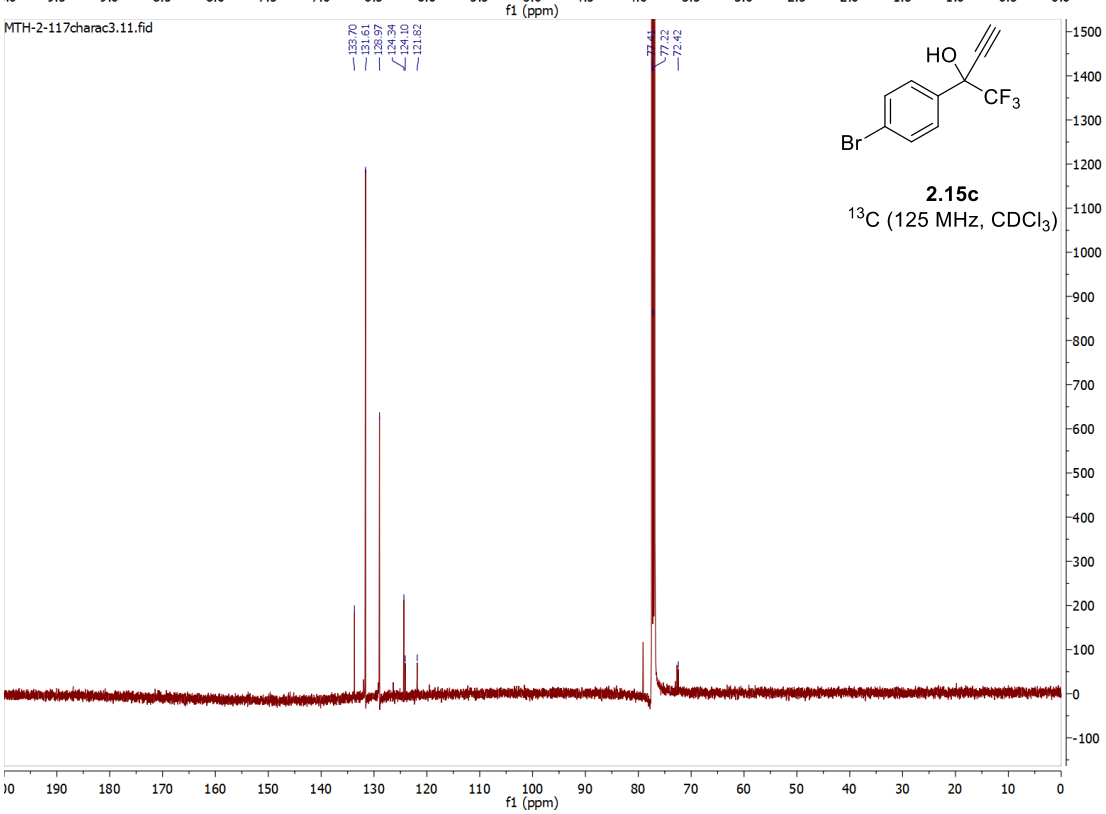
^{13}C NMR (125 MHz, CDCl3) δ: 133.7, 131.6, 129.0, 124.3, 123.0 (q, J = 285 Hz), 77.1, 77.2, 72.6 (q, J = 32.7 Hz).

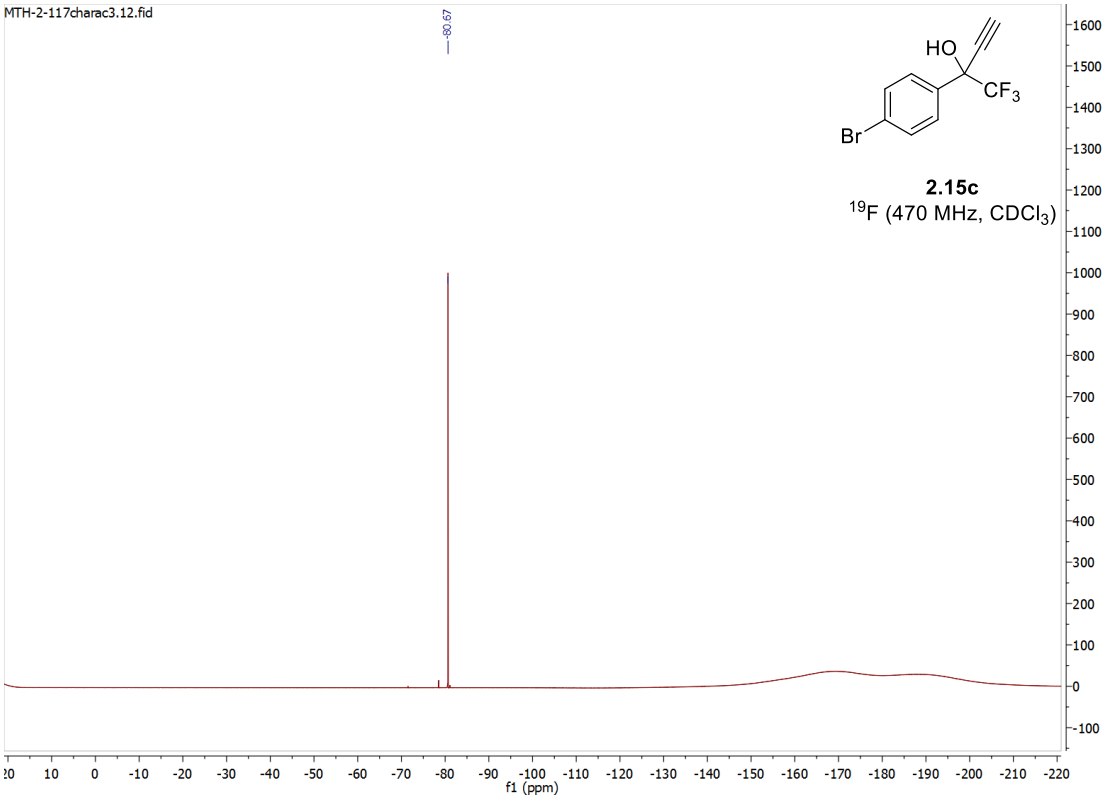
^{19}F NMR (470 MHz, CDCl3) δ: -80.7.

HRMS (CI+, m/z) for C10H6OF3Br: calcd. = 277.9554; found = 277.9557.

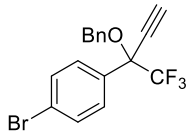
FTIR (neat): 3456, 3299, 2970, 2357, 2128, 1489, 1175, 1091, 1074, 1009, 920, 747 cm^{-1}


MTH-2-117charac3.10.fid
HO
CF3
Br
2.15c
1H (500 MHz, CDCl3)
2.00
2.02
1.03
0.99
f1 (ppm)


MTH-2-117charac3.11.fid
133.70
131.61
128.97
124.34
124.10
121.82
77.41
77.22
72.42
HO
CF3
Br
2.15c
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-117charac3.12.fid
-80.67
HO
CF3
Br
2.15c
19F (470 MHz, CDCl3)
f1 (ppm)

1-(2-(benzyloxy)-1,1,1-trifluorobut-3-yn-2-yl)-4-bromobenzene (2.16c)



2.16c

Tertiary propargylic alcohol **2.15c** (1.98 g, 7.1 mmol) was subjected to general procedure E. Upon flash column chromatography (SiO_2, pentane), the title compound **2.16c** (1.55 g, 4.2 mmol) was obtained as a light yellow oil in 59% yield.

R_f = 0.16 (pentane).

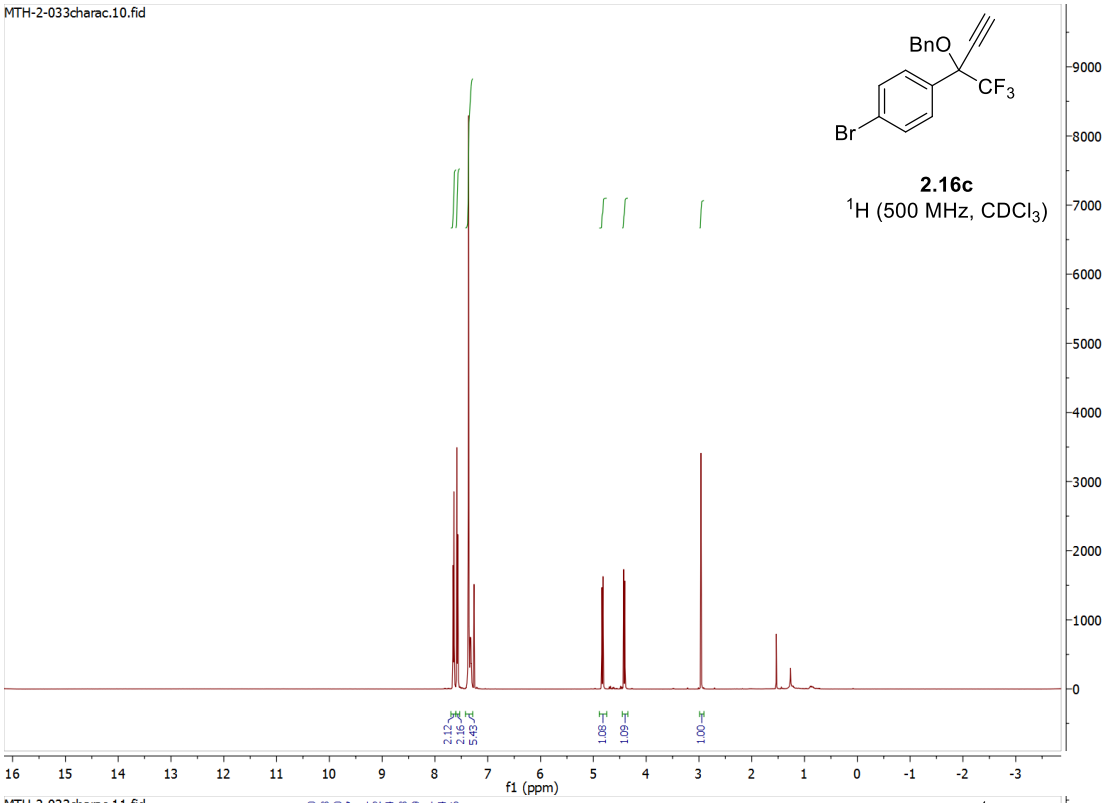
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.39-7.30 (m, 5H), 4.83 (d, *J* = 11 Hz, 1H), 4.41 (d, *J* = 11 Hz, 1H), 2.96 (s, 1H).

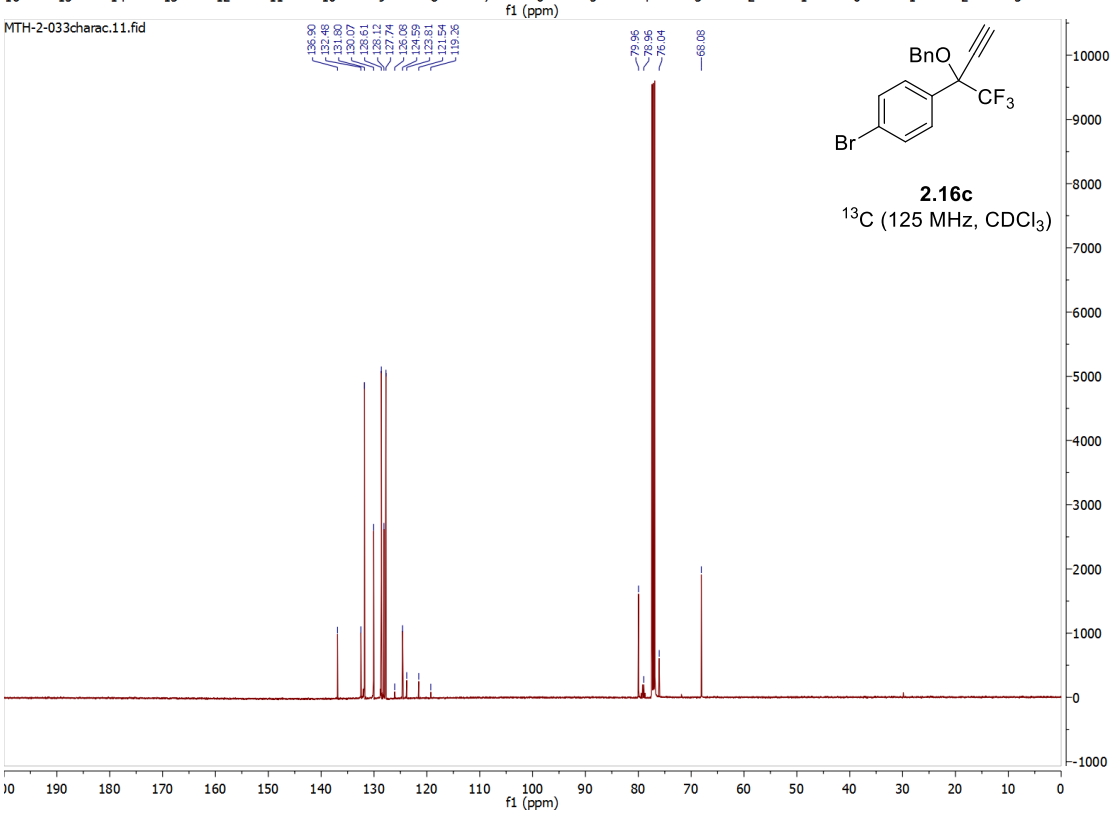
^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.9, 132.5, 131.8, 130.1, 128.6, 128.1, 127.7, 124.6, 122.7 (q, *J* = 285 Hz), 80.0, 79.0 (q, *J* = 35 Hz), 76.0, 68.1.

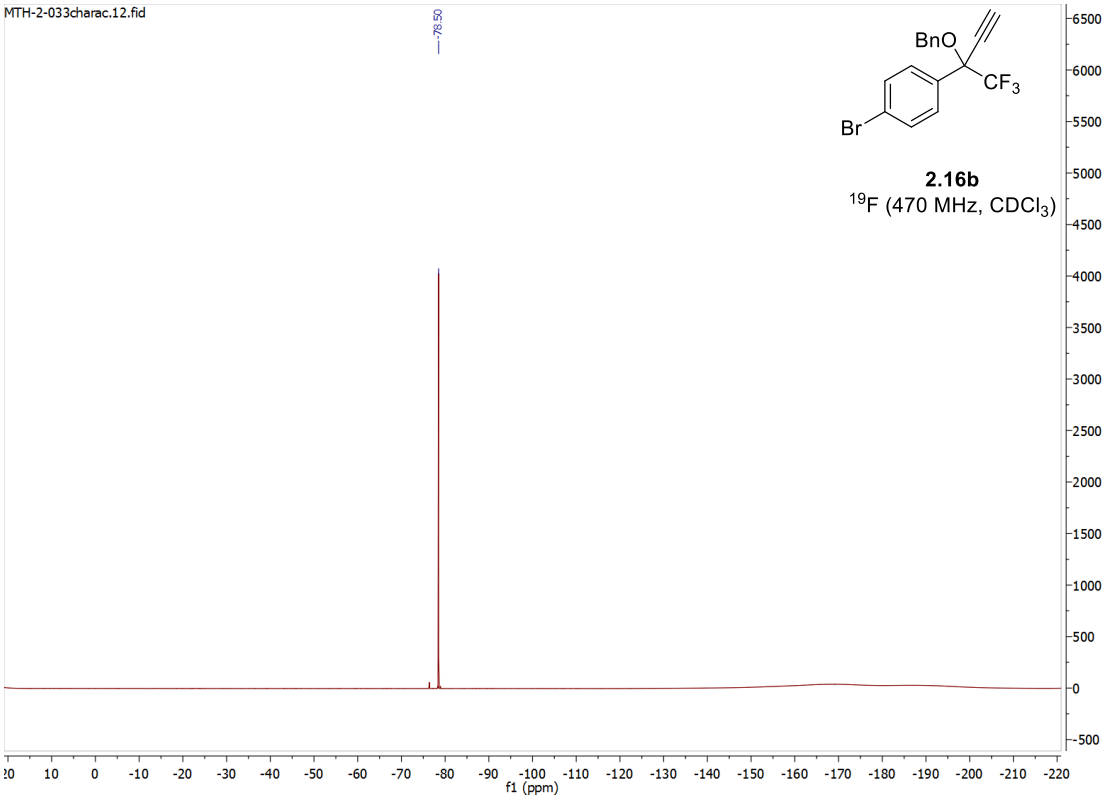
^{19}F NMR (470 MHz, $CDCl_3$) δ: -78.5.

HRMS (CI+, *m/z*) for $C_{17}H_{12}OF_3Br$: calcd = 368.0024; found = 368.0021.

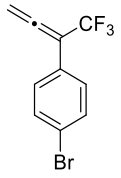
FTIR (neat): 3299, 3035, 2364, 2120, 1589, 1487, 1272 1176, 1061, 1013, 821 cm^{-1}.


MTH-2-033charac.10.fid
BnO
CF3
Br
2.16c
1H (500 MHz, CDCl3)
2.12
2.16
5.43
1.08
1.09
1.00
f1 (ppm)


MTH-2-033charac.11.fid
136.90
132.48
131.60
130.07
128.61
128.12
127.74
126.08
124.59
123.81
121.54
119.26
79.96
78.96
78.04
68.08
BnO
CF3
Br
2.16c
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-033charac.12.fid
-78.50
BnO
CF3
Br
2.16b
19F (470 MHz, CDCl3)
f1 (ppm)

1-bromo-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (2.1c)



2.1c

Benzyl protected propargylic alcohol **2.16c** (304 mg, 0.82 mmol) was subjected to general procedure F. Upon flash column chromatography (SiO_2, pentane), the title compound **2.1c** (187 mg, 0.71 mmol) was obtained as a light yellow oil in 87% yield.

R_f = 0.51 (pentane).

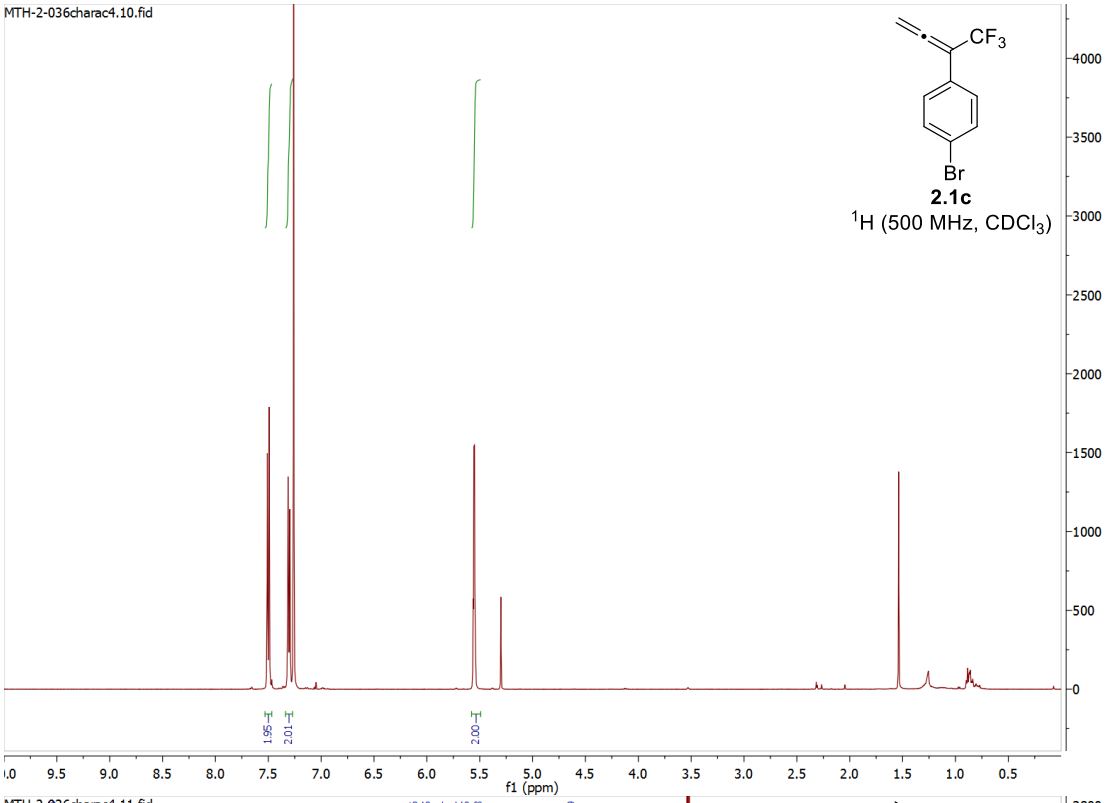
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 5.55 (q, *J* = 3.5 Hz, 2H).

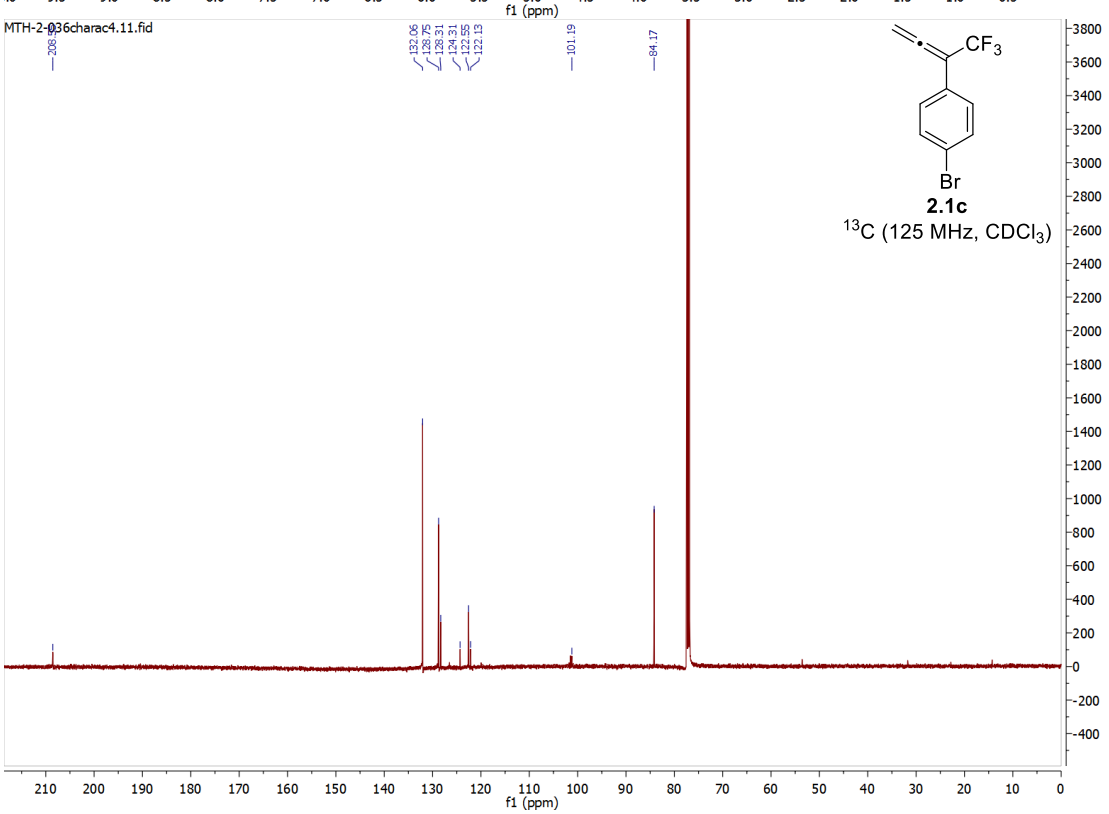
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.5 (q, *J* = 4.1 Hz), 132.1, 128.8, 128.3, 123.3 (q, *J* = 269 Hz), 122.6, 101.3 (q, *J* = 40.4 Hz), 84.2.

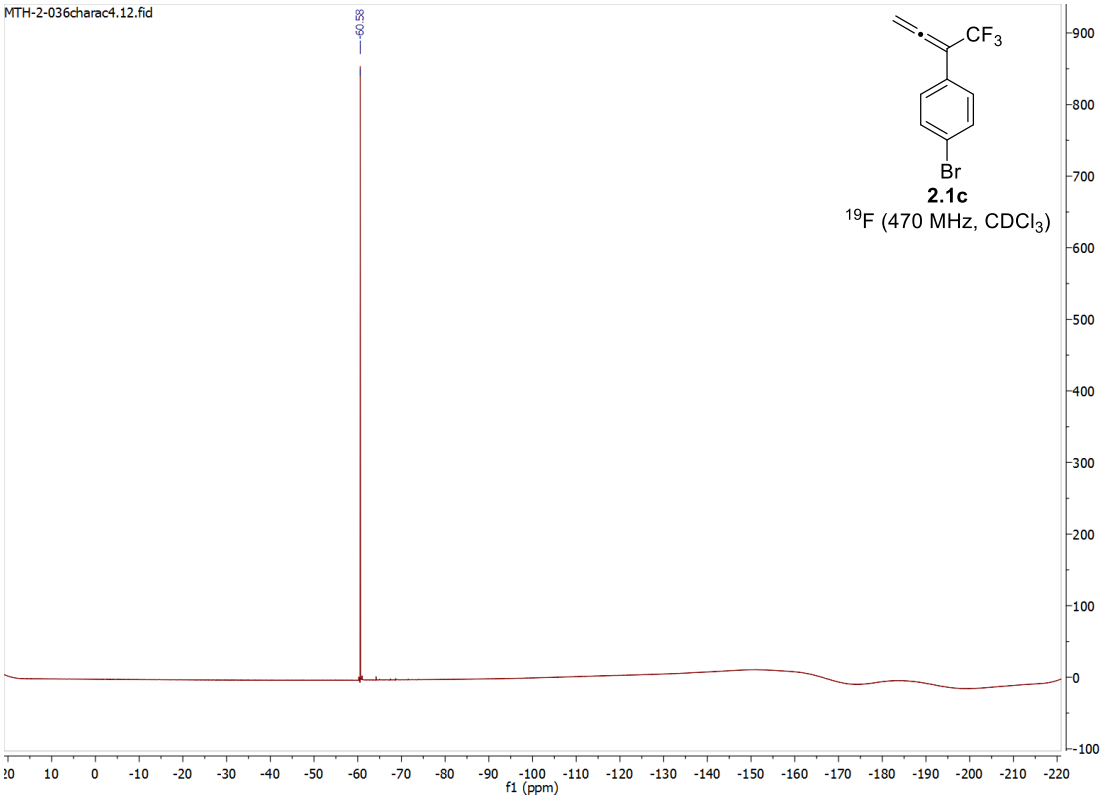
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.6.

HRMS (CI+, *m/z*) for $C_{10}H_6F_3Br$: calcd = 261.9605; found = 261.9613.

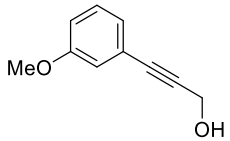
FTIR (neat): 2970, 2358, 1971, 1936, 1491, 1317, 1302, 1173, 1123, 1100, 936, 826, 745 cm^{-1}.


MTH-2-036charac4.10.fid
CF3
Br
2.1c
1H (500 MHz, CDCl3)
1.95
2.01
2.00
f1 (ppm)


MTH-2-036charac4.11.fid
208.
132.06
128.75
128.31
124.31
122.55
122.13
101.19
84.17
CF3
Br
2.1c
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-036charac4.12.fid
-60.58
CF3
Br
2.1c
19F (470 MHz, CDCl3)
f1 (ppm)

3-(3-methoxyphenyl)prop-2-yn-1-ol (2.13e)

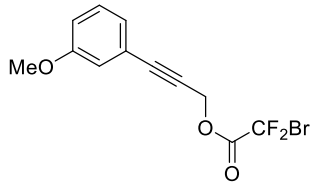


2.13e

3-Iodoanisole (2.34 g, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:3 EtOAc/hexanes), the title compound **2.13e** (1.44 mg, 0.89 mmol) was obtained as a brown solid in 89% yield.

The spectral data recorded for this compound was in complete agreement with the literature.[52]

3-(3-methoxyphenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14e)



2.14e

Propargyl alcohol **2.13e** (405 mg, 2.5 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:20 EtOAc/hexanes), the title compound **2.14e** (408 mg, 1.28 mmol) was obtained as a light yellow oil in 51% yield.

R_f = 0.54 (1:4 EtOAc/hexanes).

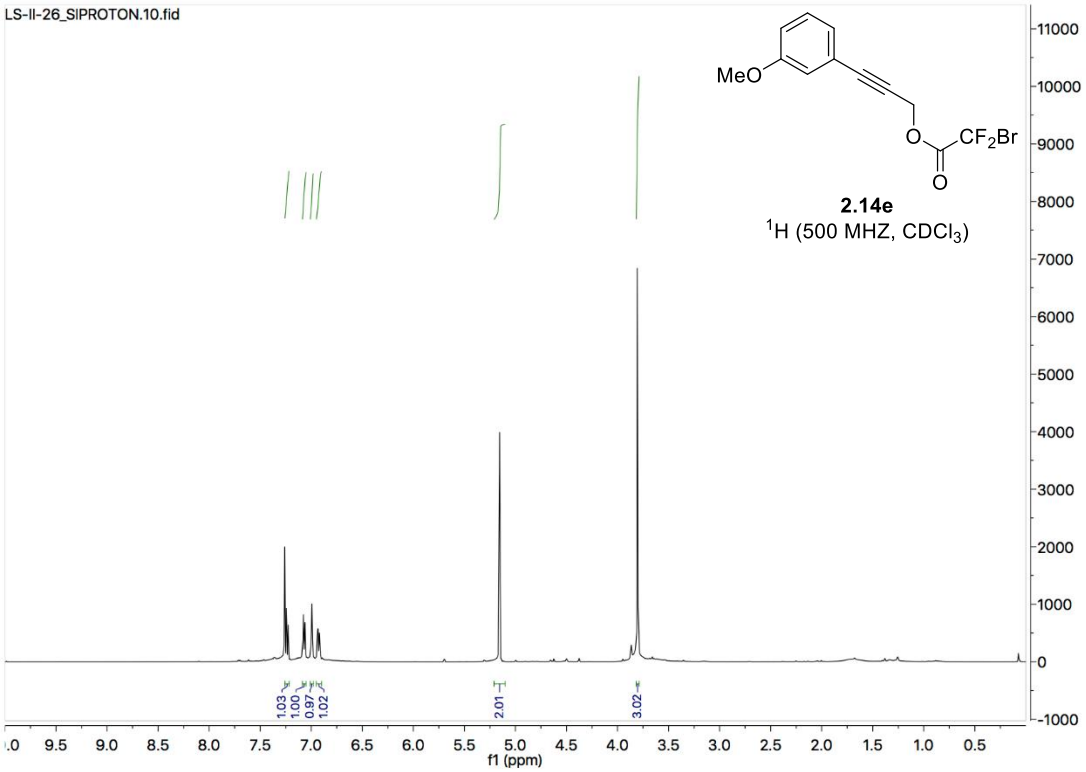
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 6.93 (dd, *J* = 2.1, 8.3 Hz, 1H), 5.16 (s, 2H), 3.81 (s, 3H).

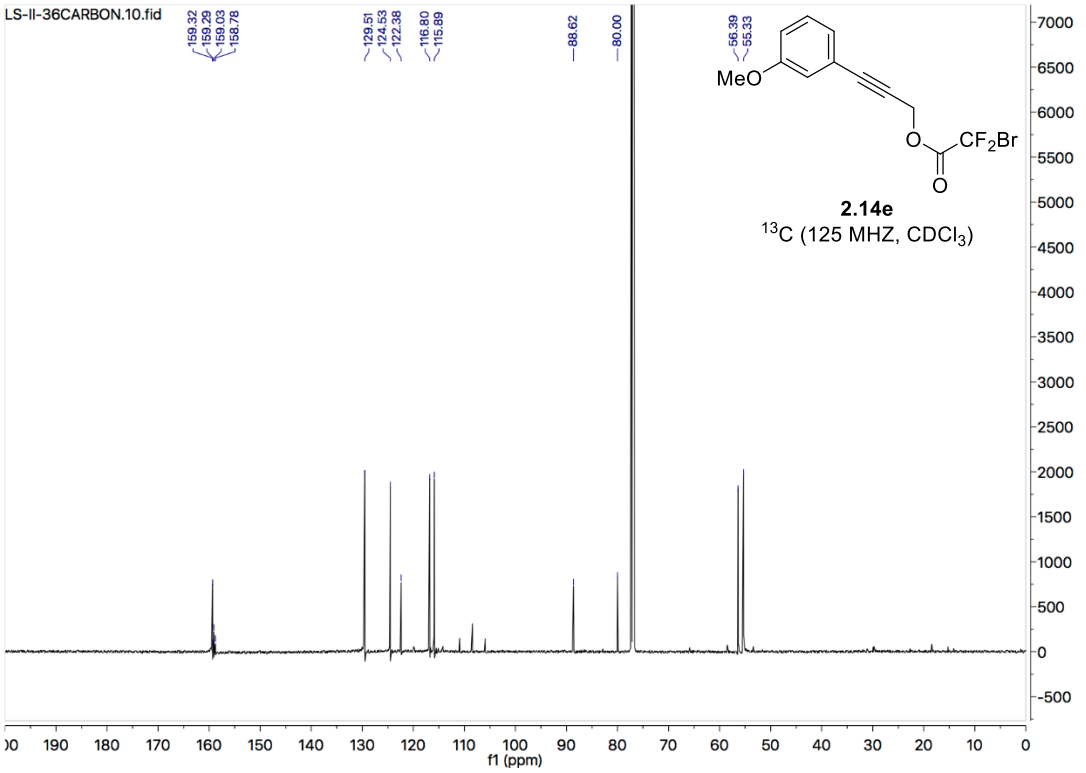
^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.3, 159.0 (t, *J* = 32.1 Hz), 129.5, 124.5, 122.4, 116.8, 115.9, 108.4, (t, *J* = 315.1 Hz), 88.6, 80.0, 56.4, 55.3.

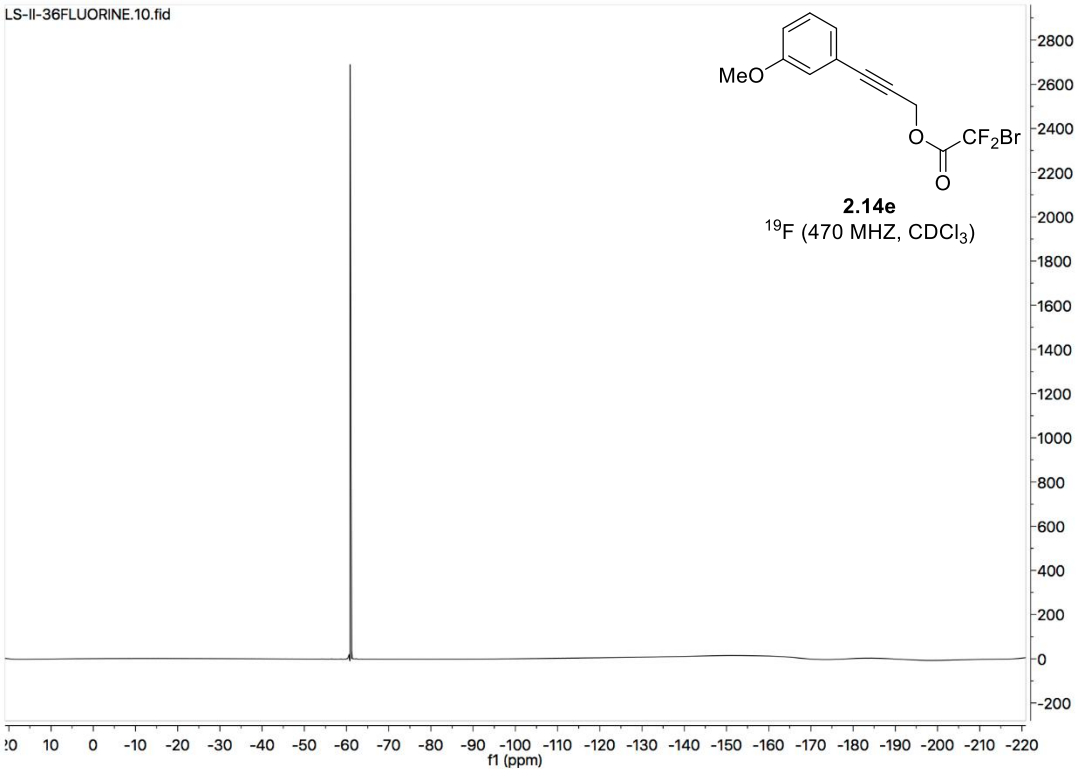
^{19}F NMR (470 MHz, $CDCl_3$) δ:-60.8.

HRMS (CI+, *m/z*) for $C_{12}H_9BrFO_3$: calcd = 317.9703; found = 317.9703.

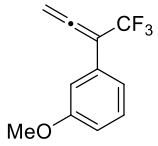
FTIR (neat): 2940, 2836, 2359, 2241, 1780, 1597, 1576, 1289, 1206, 1167, 1121, 1046, 951, 687 cm^{-1}.


LS-II-26_SIPROTON.10.fid
MeO
O
CF2Br
O
2.14e
1H (500 MHZ, CDCl3)
1.03
1.00
0.97
1.02
2.01
3.02
f1 (ppm)


LS-II-36CARBON.10.fid
159.32
159.29
159.03
158.78
129.51
124.53
122.38
116.80
115.89
88.62
80.00
56.39
55.33
MeO
O
CF2Br
O
2.14e
13C (125 MHZ, CDCl3)
f1 (ppm)


LS-II-36FLUORINE.10.fid
MeO
O
CF2Br
O
2.14e
19F (470 MHZ, CDCl3)
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

1-methoxy-3-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (2.1e)

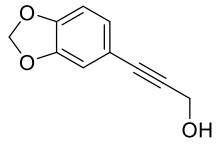


2.1e

Progargyl bromodifluoroacetate **2.14e** (363 mg, 1.14 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, 3:97 CH_2Cl_2:pentane), the title compound **2.1e** (190 mg, 0.89 mmol) was obtained as a colourless oil in 78% yield.

The spectral data recorded for this compound was in complete agreement with the literature.[51]

3-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-ol (2.13f)

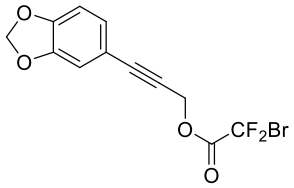


2.13f

5-Iodo-1,3-benzodioxole (1.27 mL, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:5 to 1:2 EtOAc/hexanes), the title compound **2.13f** (1.62 g, 9.2 mmol)) was obtained as a brown solid in 92% yield.

The spectral data recorded for this compound was in complete agreement with the literature.[53]

3-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14f)



2.14f

Propargyl alcohol **2.13f** (441 mg, 2.5 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:20 EtOAc/hexanes), the title compound **2.14f** (636 mg, 1.91 mmol) was obtained as a light yellow oil in 76% yield.

R_f = 0.71 (1:4 EtOAc/hexanes).

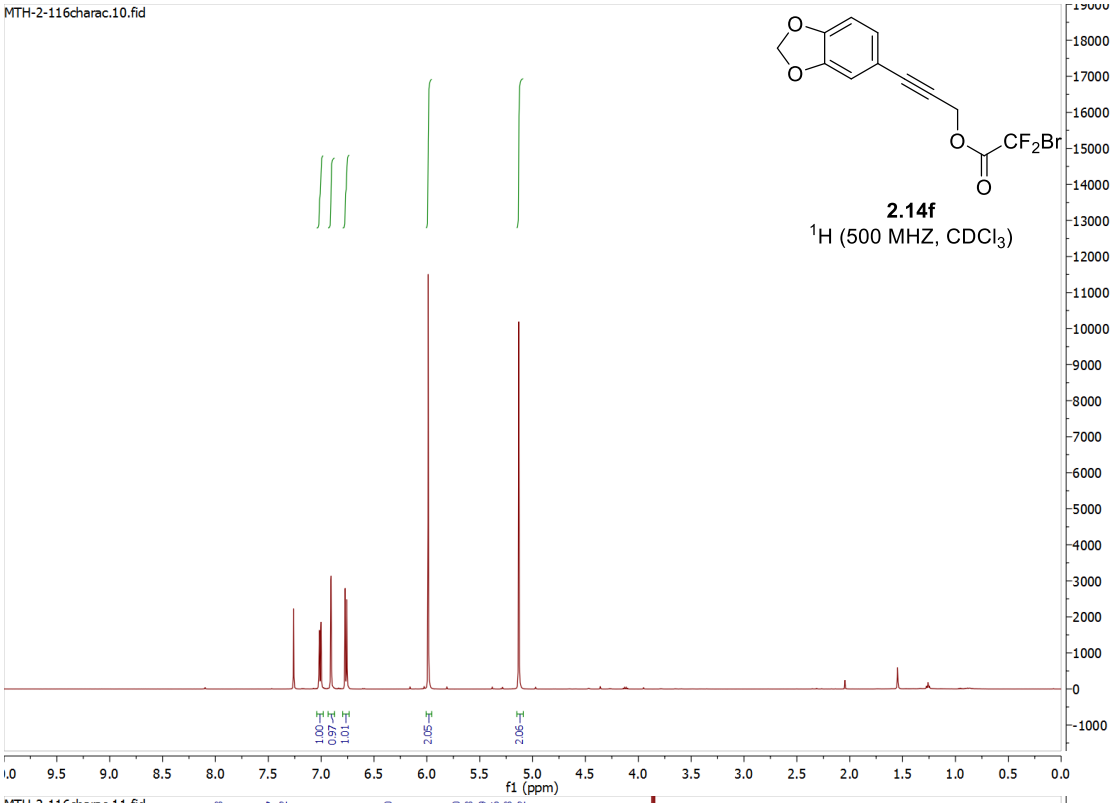
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.01 (dd, *J* = 1.1, 8.1 Hz, 1H), 6.91 (d, *J* = 1.1 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.99 (s, 2H), 5.13 (s, 2H).

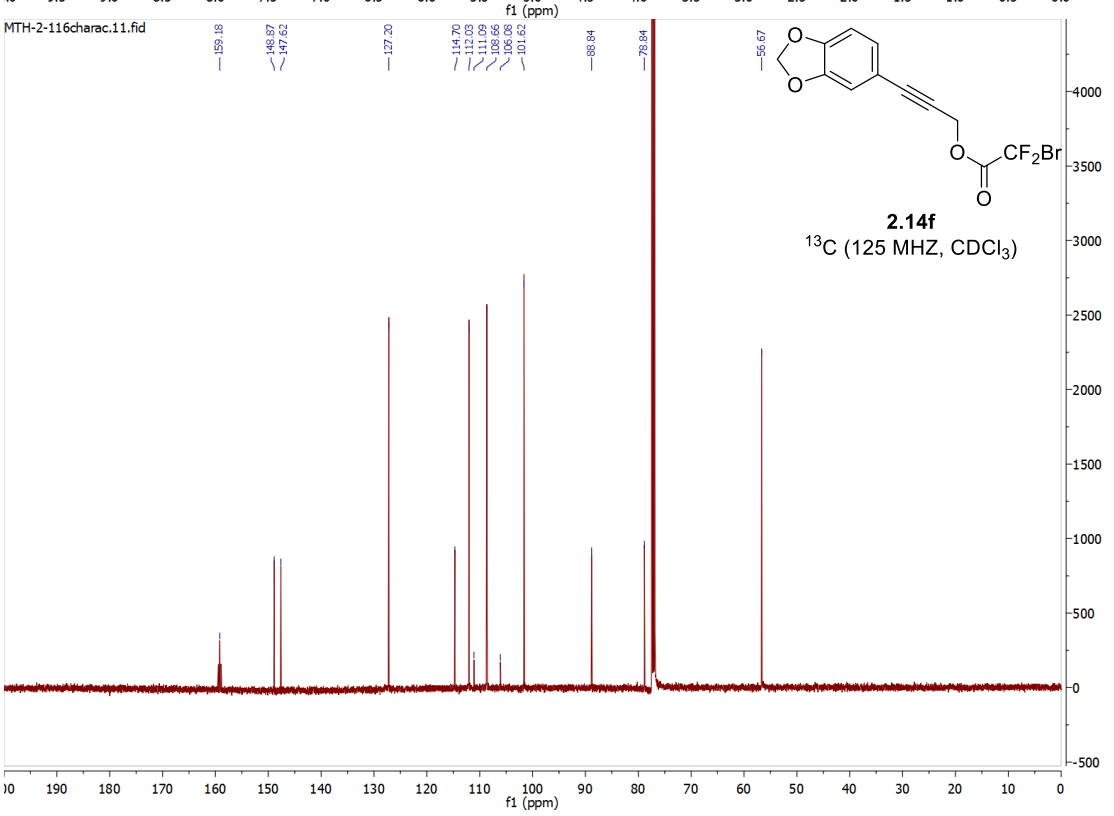
^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.2 (t, *J* = 31.9 Hz), 148.9, 147.6, 127.2, 114.7, 112.0, 108.7, 108.6 (t, *J* = 315.0 Hz), 101.6, 88.8, 78.7, 56.7.

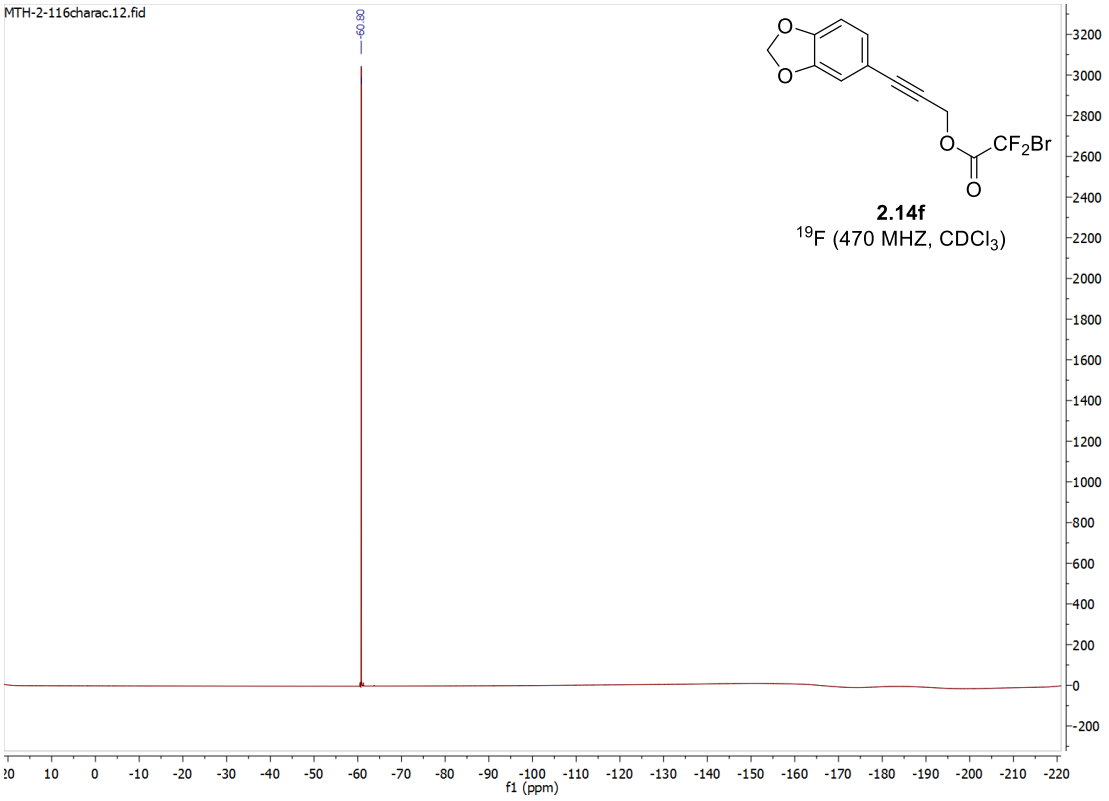
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.9.

HRMS (CI+, *m/z*) for $C_{12}H_7BrF_2O_4$: calcd. = 331.9496; found = 331.9500.

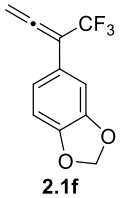
FTIR (neat): 2906, 2359, 2234, 1777, 1489, 1444, 1291, 1214, 1037, 936, 809 cm^{-1}.


MTH-2-116charac.10.fid
O
O
O
CF2Br
O
2.14f
1H (500 MHZ, CDCl3)
1.00
0.97
1.01
2.05
2.06
f1 (ppm)


MTH-2-116charac.11.fid
159.18
148.87
147.62
127.20
114.70
112.03
111.09
108.66
106.08
101.62
88.84
78.84
56.67
O
O
O
CF2Br
O
2.14f
13C (125 MHZ, CDCl3)
f1 (ppm)


MTH-2-116charac.12.fid
-60.80
O
O
O
O
CF2Br
2.14f
19F (470 MHZ, CDCl3)
f1 (ppm)

5-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzo[d][1,3]dioxole (2.1f)



2.1f

Progargyl bromodifluoroacetate **2.14f** (411 mg, 1.23 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, 3:97 CH_2Cl_2:pentane), the title compound **2.1f** (201 mg, 0.89 mmol) was obtained as a light yellow oil in 72% yield.

R_f = 0.24 (hexanes).

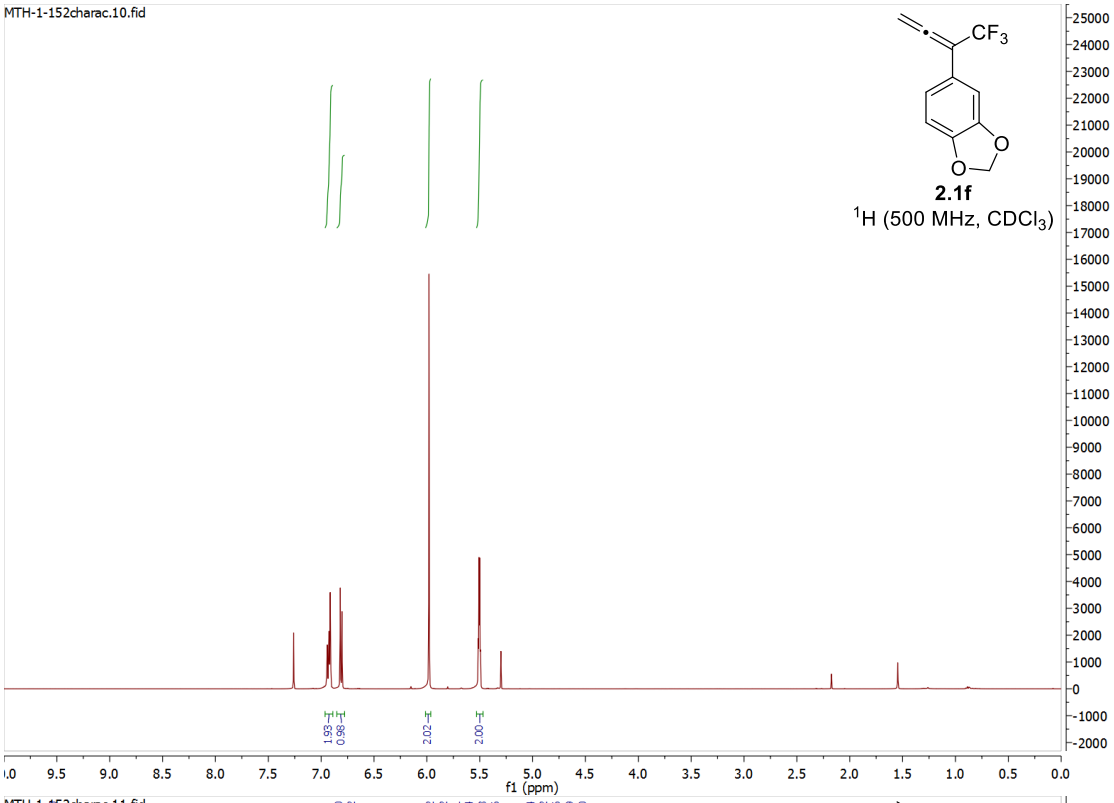
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.93 (d, *J* = 8.8 Hz, 1H), 6.91 (s, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.98 (s, 2H), 5.50 (q, *J* = 3.3 Hz, 2H).

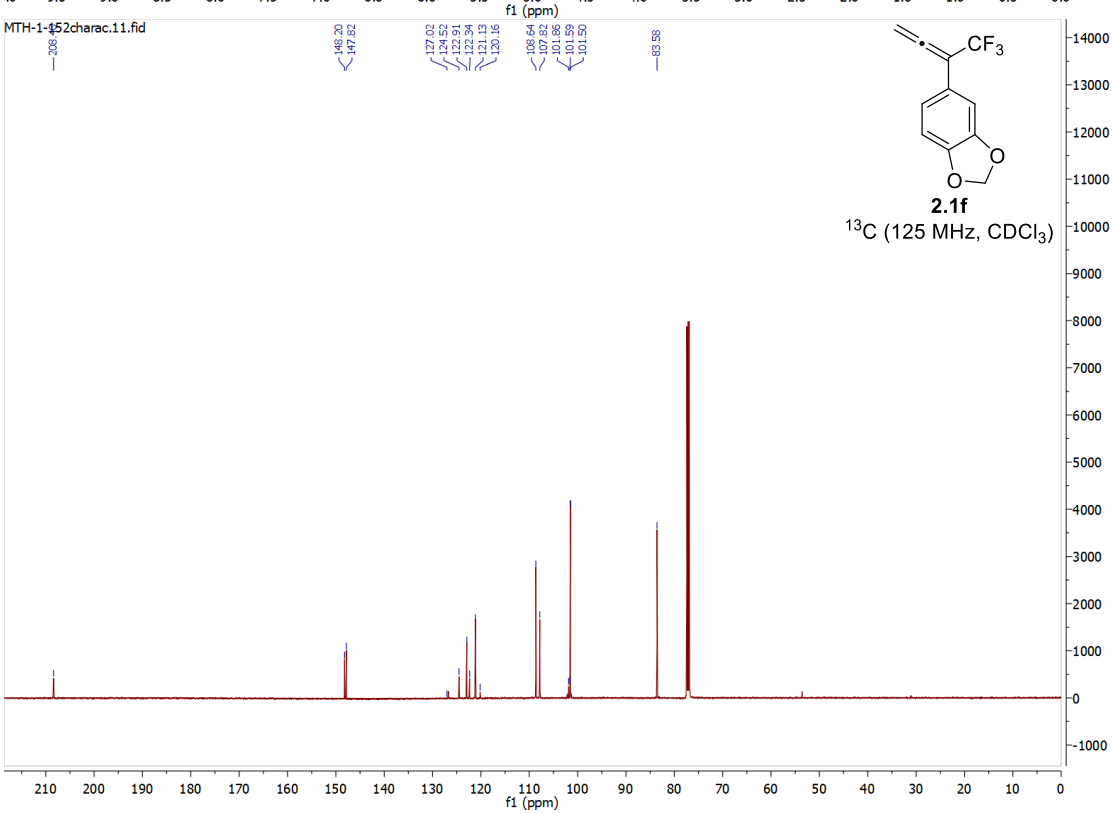
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.4 (q, *J* = 4.0 Hz), 148.2, 147.8, 123.3 (q, *J* = 274 Hz), 122.9, 121.1, 109.6, 107.8, 101.7 (q, *J* = 34.7 Hz), 101.5, 83.6.

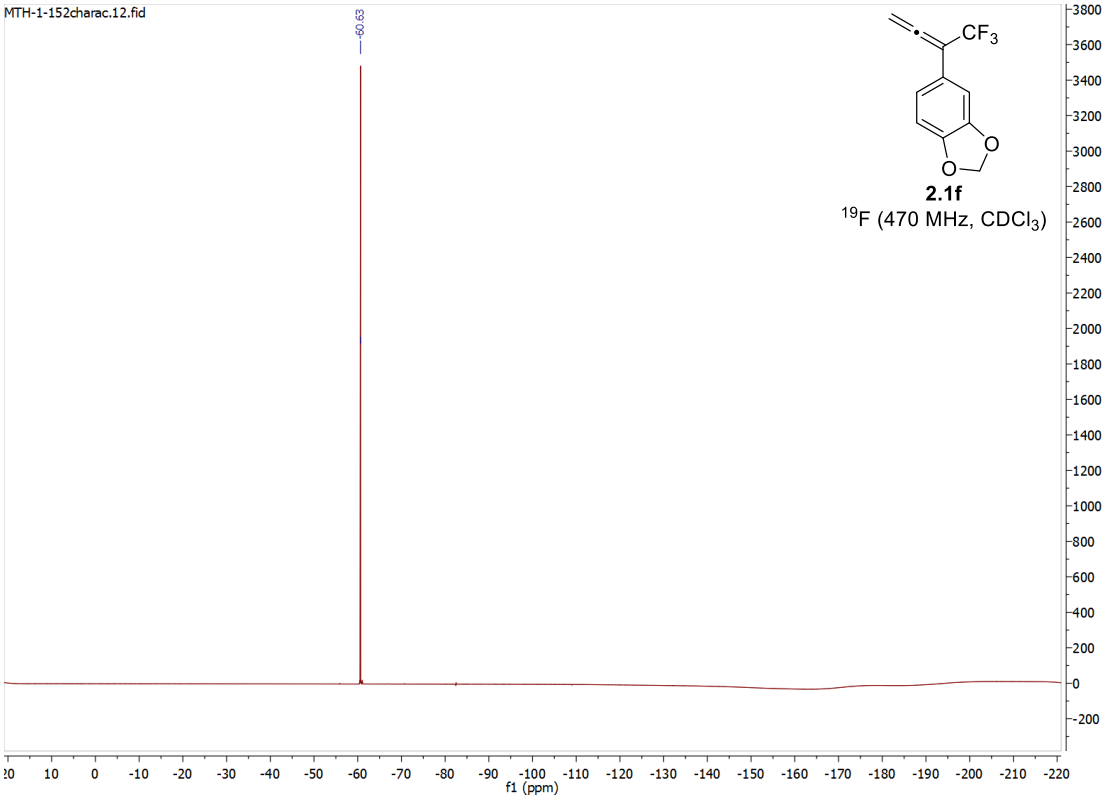
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.6.

HRMS (CI+, *m/z*) for $C_{11}H_6O_2F_3$: calcd. = 227.0320; found = 227.0318.

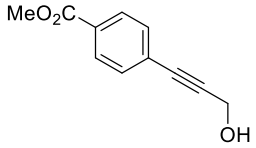
FTIR (neat): 2900, 2360, 1970, 1611, 1506, 1490, 1305, 1231, 1110, 1086, 1039, 936, 864, 807 cm^{-1}.


MTH-1-152charac.10.fid
CF3
O
O
2.1f
1H (500 MHz, CDCl3)
1.93
0.98
2.02
2.00
f1 (ppm)


MTH-1-152charac.11.fid
208.
148.20
147.82
127.02
124.52
122.91
122.34
121.13
120.16
108.64
107.82
101.86
101.59
101.50
83.58
CF3
O
O
2.1f
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-1-152charac.12.fid
-60.63
CF3
O
O
2.1f
19F (470 MHz, CDCl3)
f1 (ppm)

Methyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate (2.13g)

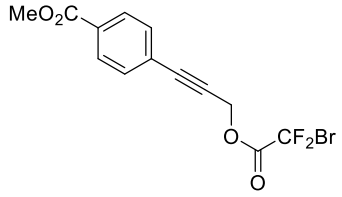


2.13g

Methyl-4-iodobenzoate (2.62 g, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:5 to 1:2 EtOAc/hexanes), the title compound **2.13g** (1.49 g, 7.8 mmol) was obtained as a brown solid in 78% yield.

The spectral data recorded for this compound was in complete agreement with the literature.[54]

Methyl 4-(3-(2-bromo-2,2-difluoroacetoxy)prop-1-yn-1-yl)benzoate (2.14g)



2.14g

Propargyl alcohol **2.13g** (476 mg, 2.5 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:15 EtOAc/hexanes), the title compound **2.14g** (430 mg, 1.24 mmol) was obtained as a light yellow oil in 50% yield.

R_f = 0.65 (1:4 EtOAc/hexanes).

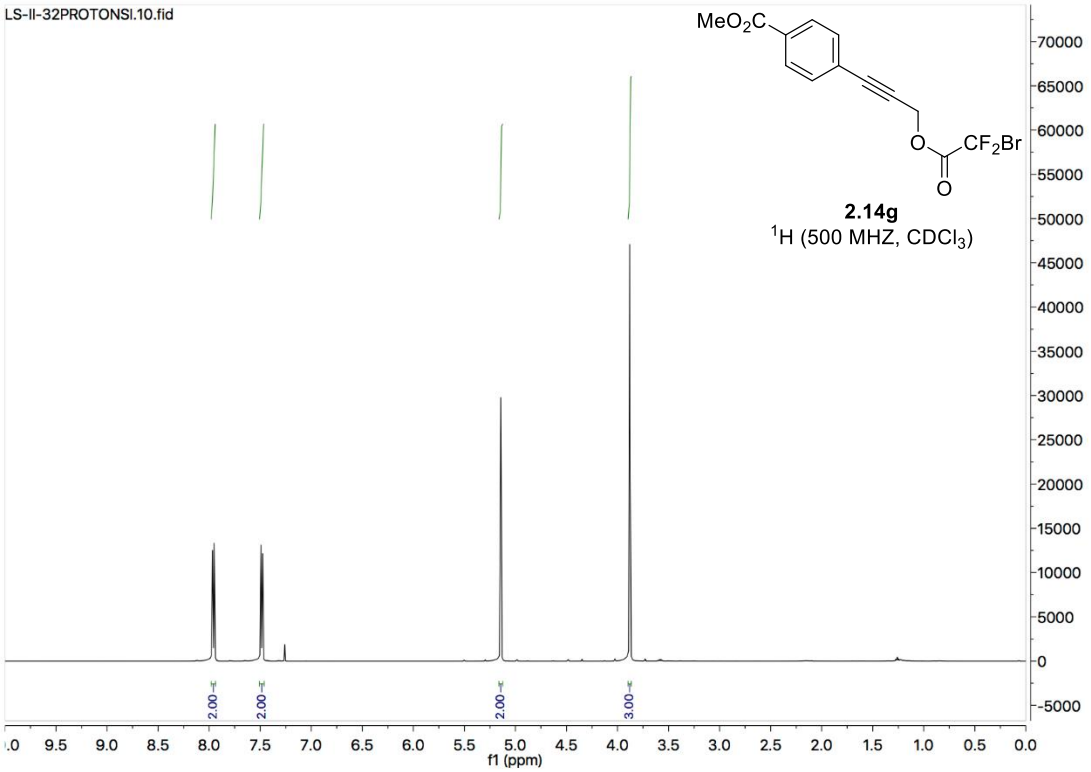
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 5.14 (s, 2H), 3.88 (s, 3H).

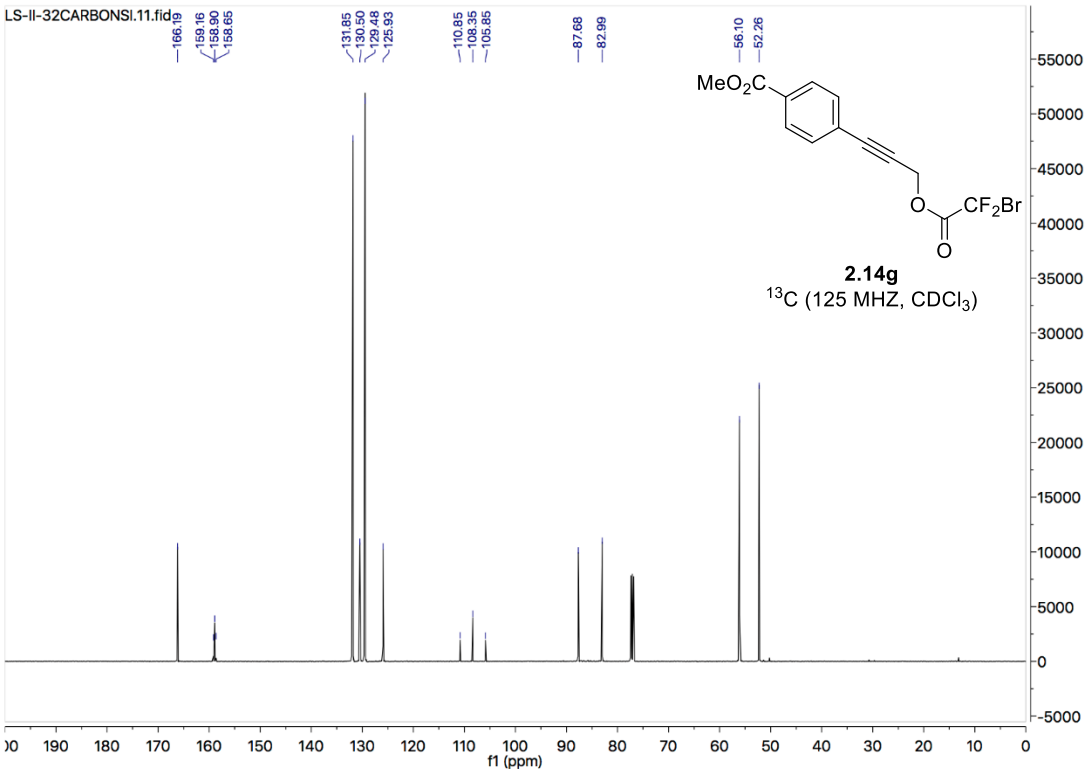
^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 158.9 (t, *J* = 32.1 Hz), 131.9, 130.5, 129.5, 125.9, 108.4 (t, *J* = 316.1 Hz), 87.7, 83.0, 56.1, 52.3.

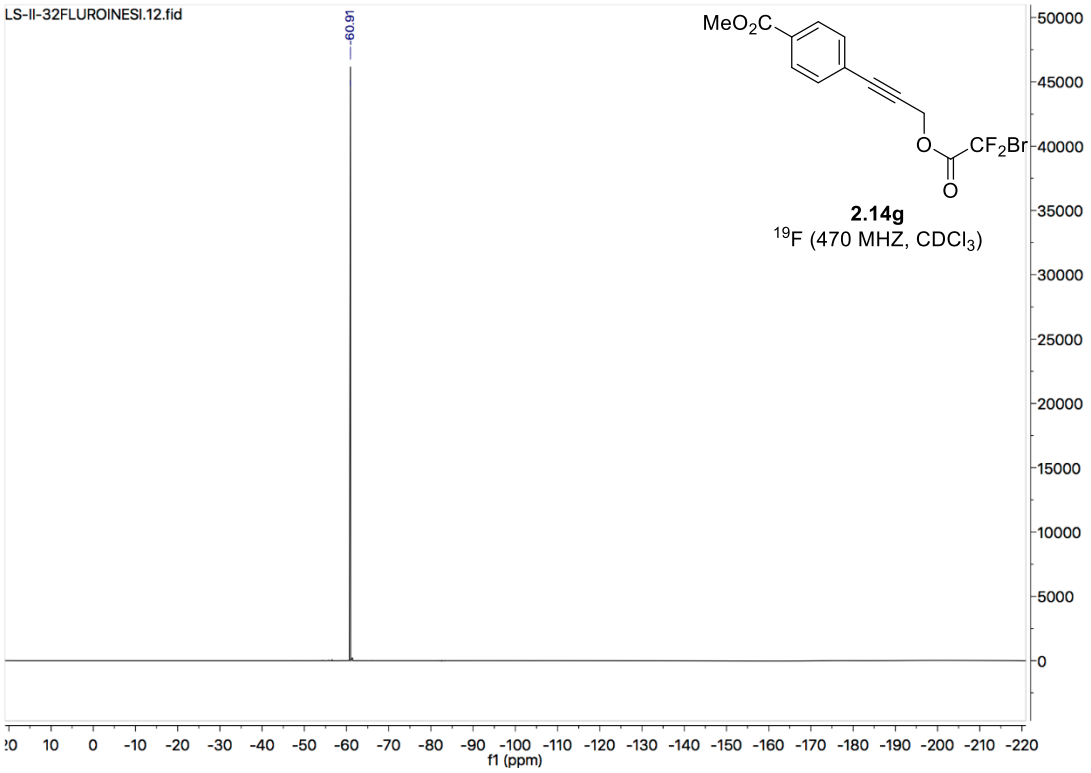
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.9.

HRMS (CI+, *m/z*) for $C_{13}H_9BrF_2O_4$: calcd. = 345.9652; found = 345.9655.

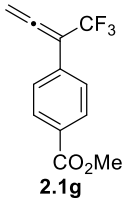
FTIR (neat): 2954, 1780, 1721, 1274, 1167, 1107, 946, 768, 695 cm^{-1}.


LS-II-32PROTONSI.10.fid
MeO2C
O
CF2Br
O
2.14g
1H (500 MHZ, CDCl3)
2.00
2.00
2.00
3.00
f1 (ppm)


LS-II-32CARBONSI.11.fid
166.19
159.16
158.90
158.65
131.85
130.50
129.48
125.93
110.85
108.35
105.85
87.68
82.99
56.10
52.26
MeO2C
O
CF2Br
O
2.14g
13C (125 MHZ, CDCl3)
f1 (ppm)


LS-II-32FLUROINESI.12.fid
-60.91
MeO2C
O
CF2Br
O
2.14g
19F (470 MHZ, CDCl3)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

Methyl 4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzoate (2.1g)



2.1g

Progargyl bromodifluoroacetate **2.14g** (360 mg, 1.03 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, 10:90 to 1:3 CH_2Cl_2:pentane), the title compound **2.1g** (204 mg, 0.84 mmol) was obtained as a colourless solid in 82% yield.

R_f = 0.09 (1:20 CH_2Cl_2/pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 7.1 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 2H), 5.62 (q, *J* = 3.1 Hz, 2H), 3.93 (s, 3H).

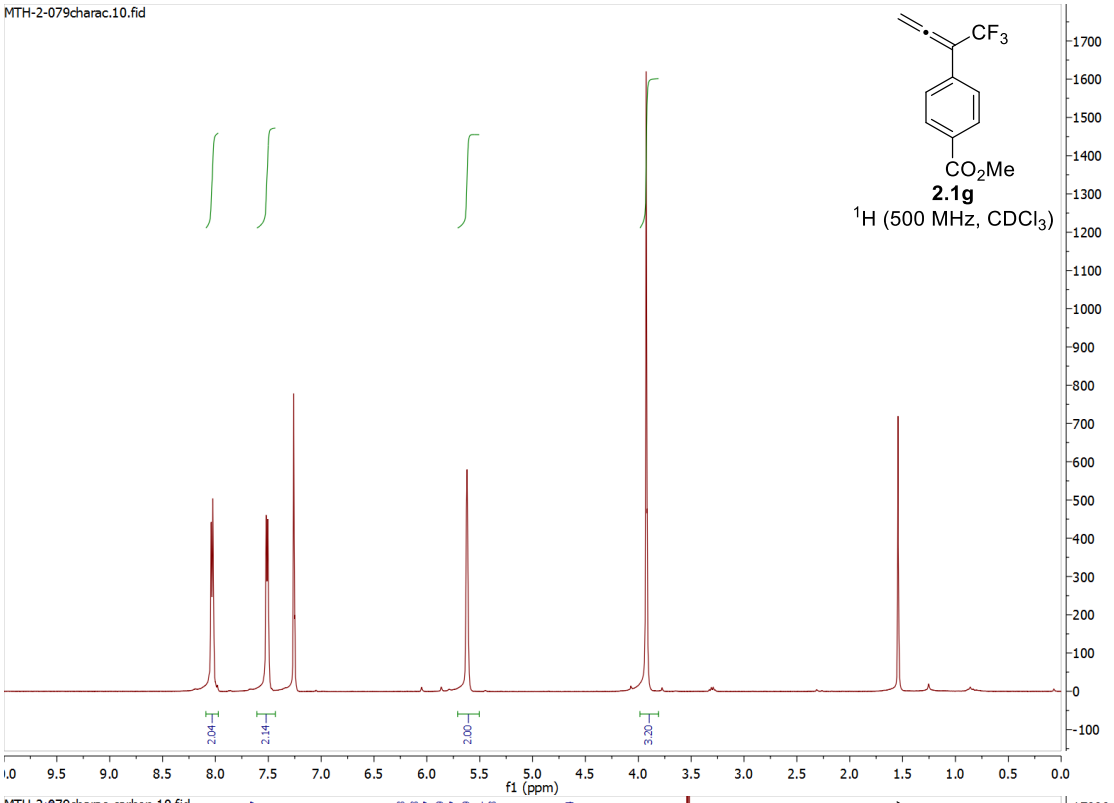
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.1 (q, *J* = 4 Hz), 166.7, 133.9, 130.1, 129.9, 127.0, 123.1 (q, *J* = 274 Hz), 101.7 (q, *J* = 36.1 Hz), 84.4, 52.4.

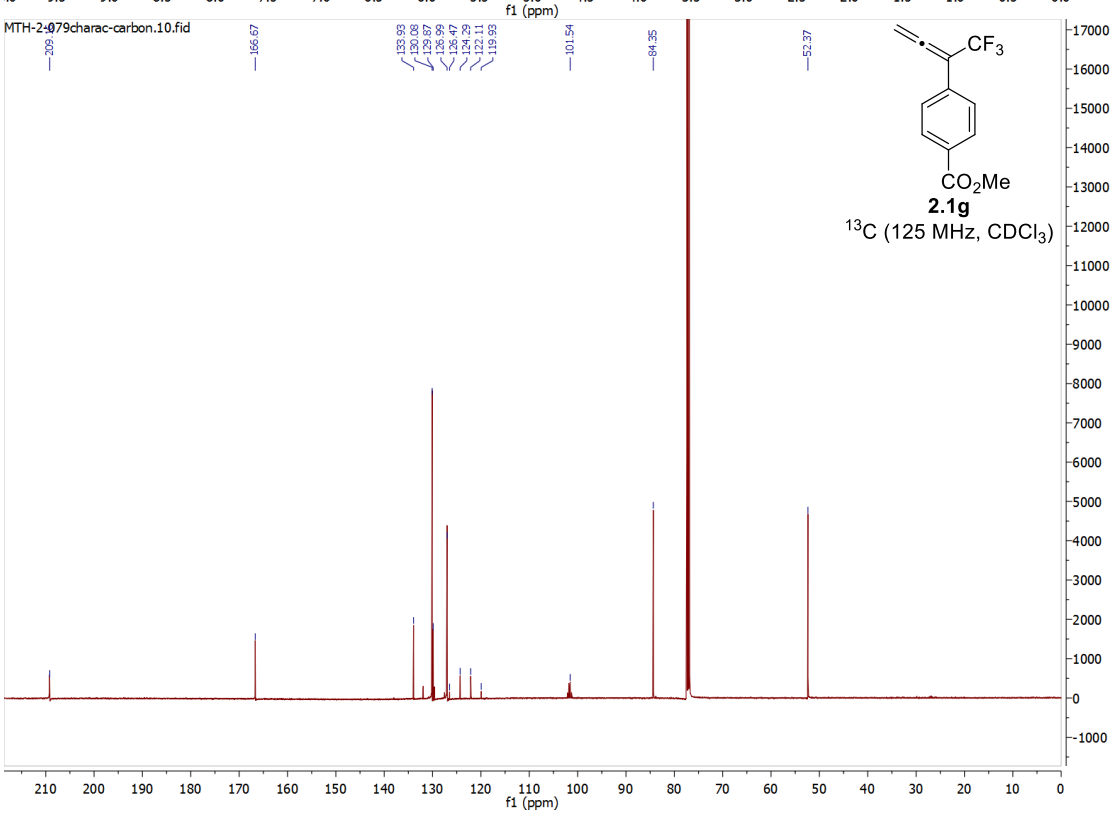
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.3.

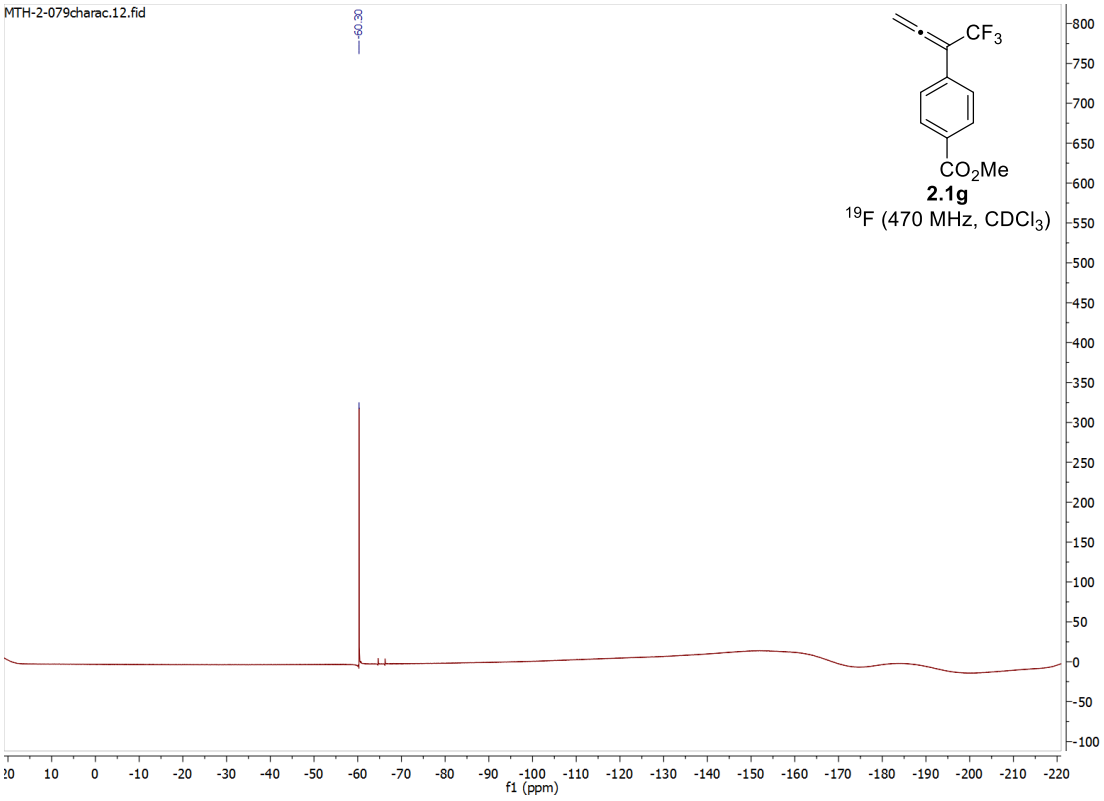
HRMS (CI+, *m/z*) for $C_{12}H_9O_2F_3$: calcd. = 242.0555; found = 242.0556.

FTIR (neat): 2954, 1970, 1936, 1711, 1613, 1432, 1260, 1119, 1094, 934, 880, 773 cm^{-1}.

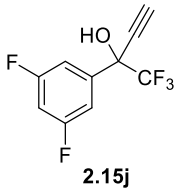
Melting Point: 55-58 °C


MTH-2-079charac.10.fid
CF3
CO2Me
2.1g
1H (500 MHz, CDCl3)
2.04
2.14
2.00
3.20
f1 (ppm)


MTH-2-079charac-carbon.10.fid
209.
166.67
133.93
130.08
129.87
126.99
126.47
124.29
122.11
119.93
101.54
84.35
52.37
CF3
CO2Me
2.1g
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-079charac.12.fid
-60.30
CF3
CO2Me
2.1g
19F (470 MHz, CDCl3)
f1 (ppm)

2-(3,5-difluorophenyl)-1,1,1-trifluorobut-3-yn-2-ol (2.15j)



2.15j

2,2,2,3',5'-pentafluoroacetophenone (1.05 g, 5.0 mmol) was subjected to general procedure D. Upon flash column chromatography (SiO_2, 1:5 Et_2O/hexanes), the title compound **2.15j** (0.97 g, 4.1 mmol) was obtained as a light yellow oil in 82% yield.

R_f = 0.43 (4:1 Hexanes:EtOAc).

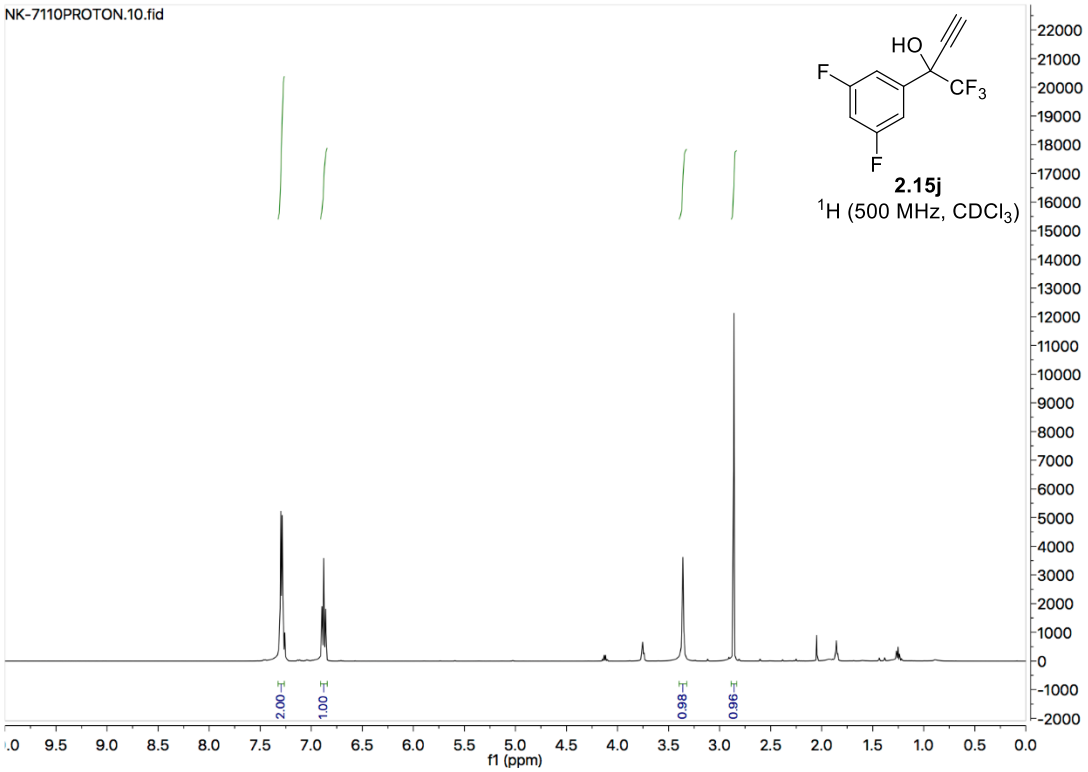
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 (br d, *J* = 6.6 Hz, 2H), 6.88 (tt, *J* = 2.3, 8.7 Hz, 1H), 3.36 (br s, 1H), 2.86 (s, 1H).

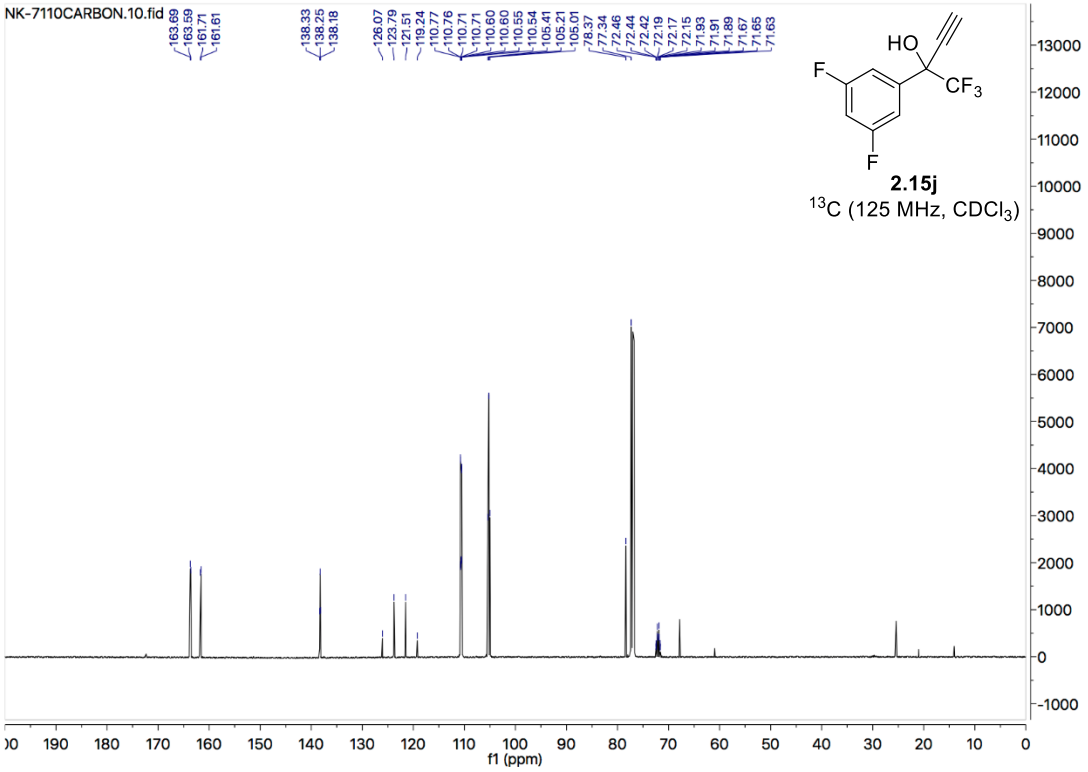
^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.7 (dd, *J* = 12.9, 249.3 Hz), 138.3 (t, *J* = 9.4 Hz), 122.7 (q, *J* = 285.8 Hz), 110.7 (m), 105.2 (t, *J* = 25.4 Hz), 78.4, 77.3, 72.0 (qt, *J* = 2.5, 33.1 Hz).

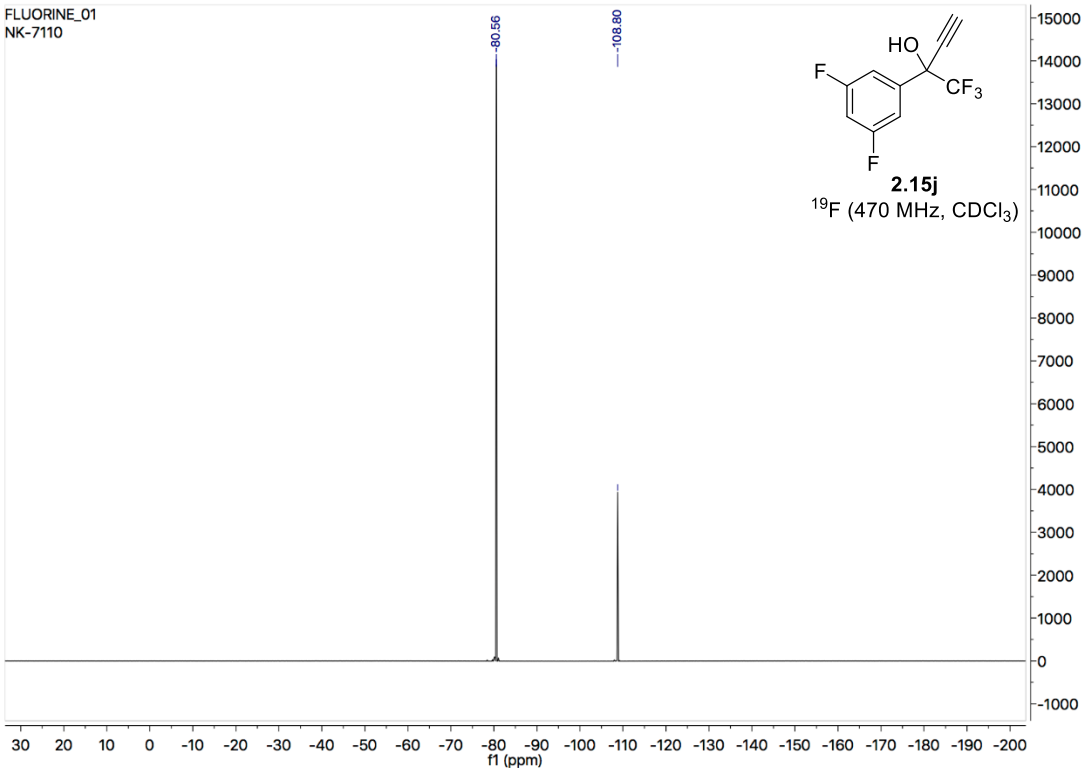
^{19}F NMR (470 MHz, $CDCl_3$) δ: -80.6, -108.8.

HRMS (CI+, *m/z*) for $C_{10}H_5F_5O$: calcd. = 236.0261; found = 236.0260.

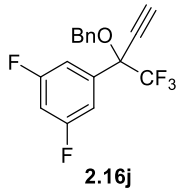
FTIR (neat): 3590, 3307, 2128, 1624, 1608, 1444, 1314, 1262, 1185, 1121, 1038, 984, 862, 811, 729. 683 cm^{-1}.


NK-7110PROTON.10.fid
HO
F
CF3
F
2.15j
1H (500 MHz, CDCl3)
2.00
1.00
0.98
0.96
f1 (ppm)


NK-7110CARBON.10.fid
163.69
163.59
161.71
161.61
138.33
138.25
138.18
126.07
123.79
121.51
119.24
110.77
110.76
110.71
110.71
110.60
110.60
110.55
110.54
105.41
105.21
105.01
78.37
77.34
72.46
72.44
72.42
72.19
72.17
72.15
71.93
71.91
71.89
71.67
71.65
71.63
HO
F
CF3
F
2.15j
13C (125 MHz, CDCl3)
f1 (ppm)


FLUORINE_01
NK-7110
-80.56
-108.80
HO
F
CF3
F
2.15j
19F (470 MHz, CDCl3)
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

1-(2-(benzyloxy)-1,1,1-trifluorobut-3-yn-2-yl)-3,5-difluorobenzene (2.16j)



2.16j

Tertiary propargylic alcohol **2.15j** (2.26g, 9.55 mmol) was subjected to general procedure E. Upon flash column chromatography (SiO_2, pentane), the title compound **2.16j** (2.65 g, 8.12 mmol) was obtained as a light yellow oil in 85% yield.

R_f = 0.8 (4:1 hexanes:EtOAc).

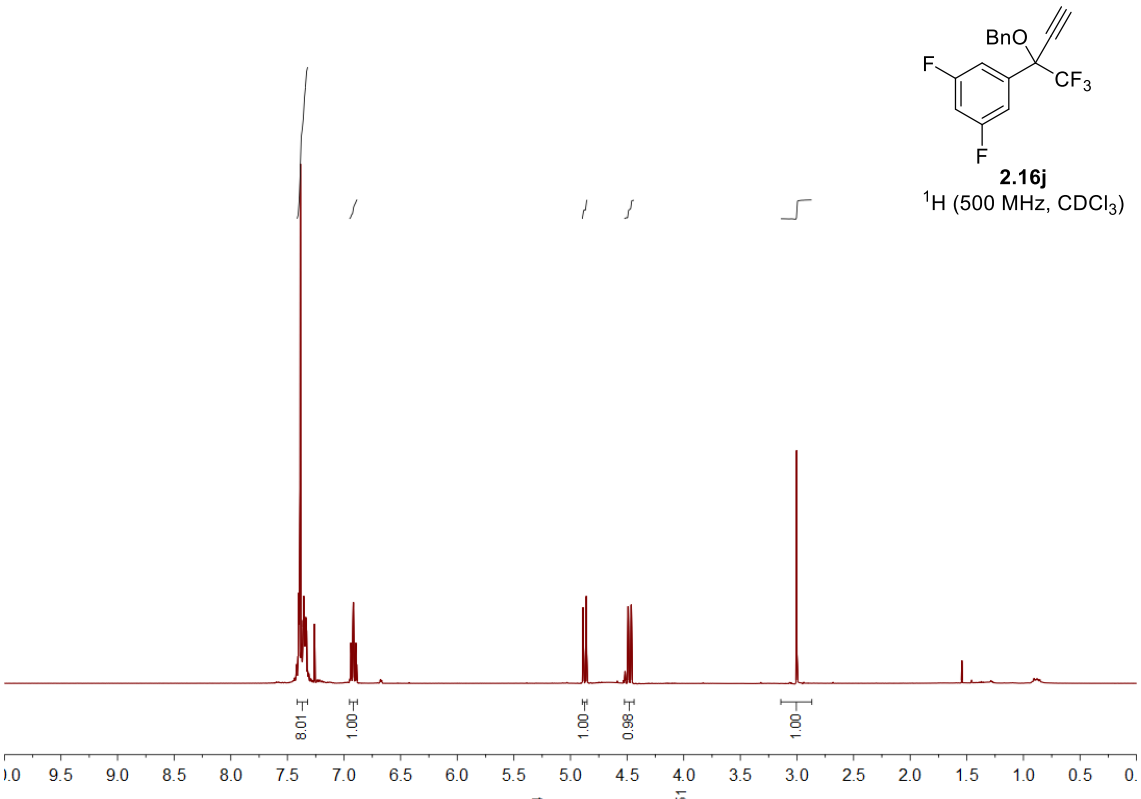
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41–7.32 (m, 8H), 6.92 (tt, *J* = 8.6, 2.3 Hz, 1H), 4.87 (d, *J* = 11 Hz, 1H), 4.48 (d, *J* = 11 Hz, 1H), 3.00 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.9 (d, *J* = 12.4 Hz), 161.9 (d, *J* = 12.4 Hz), 137.4 (t, *J* = 8.9 Hz), 136.5, 128.5, 128.2, 127.7, 122.4 (q, *J* = 285.8 Hz), 111.6 (d, *J* = 27.6 Hz), 105.6 (t, *J* = 25.3 Hz), 80.3, 78.6 (q, *J* = 32.0 Hz), 68.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -78.3, -108.5.

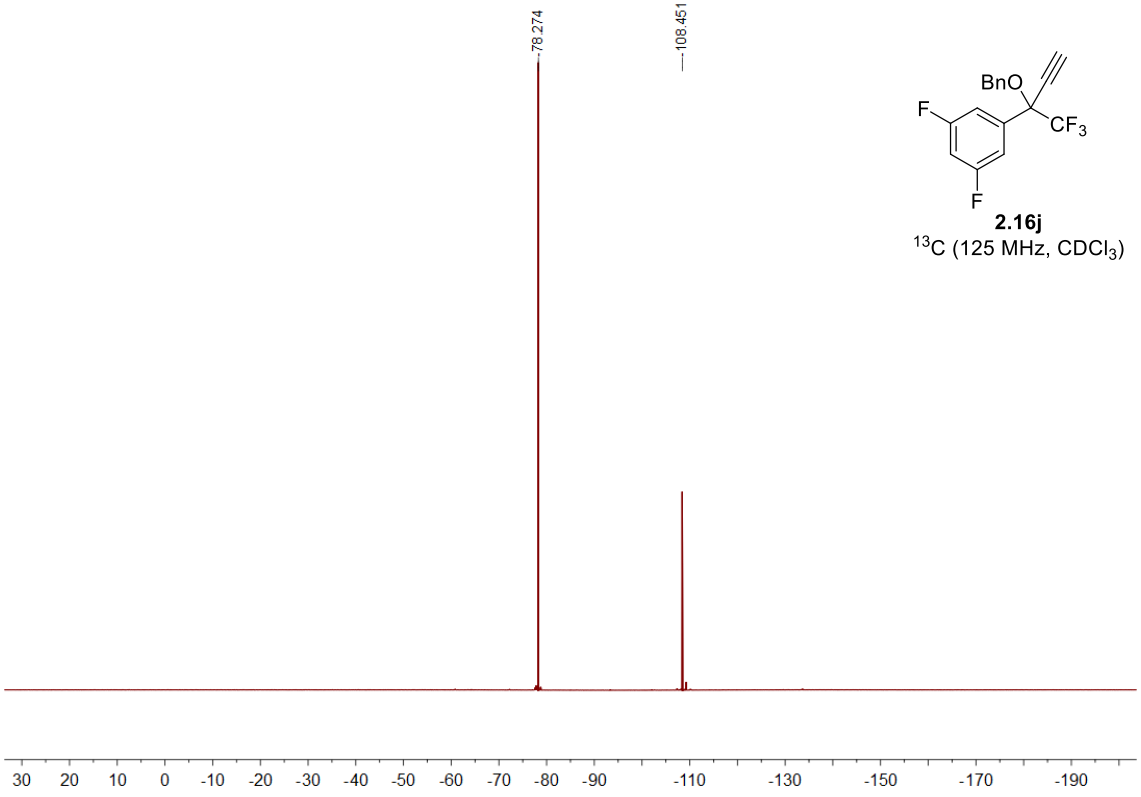
HRMS (CI+, *m/z*) for $C_{17}H_{11}F_5O$: calcd. 326.0730; found = 326.0721.

FTIR (neat): 3094, 2960, 2123, 1623, 1608, 1443, 1273, 1068, 1026, 863, 732, 671 cm^{-1}.



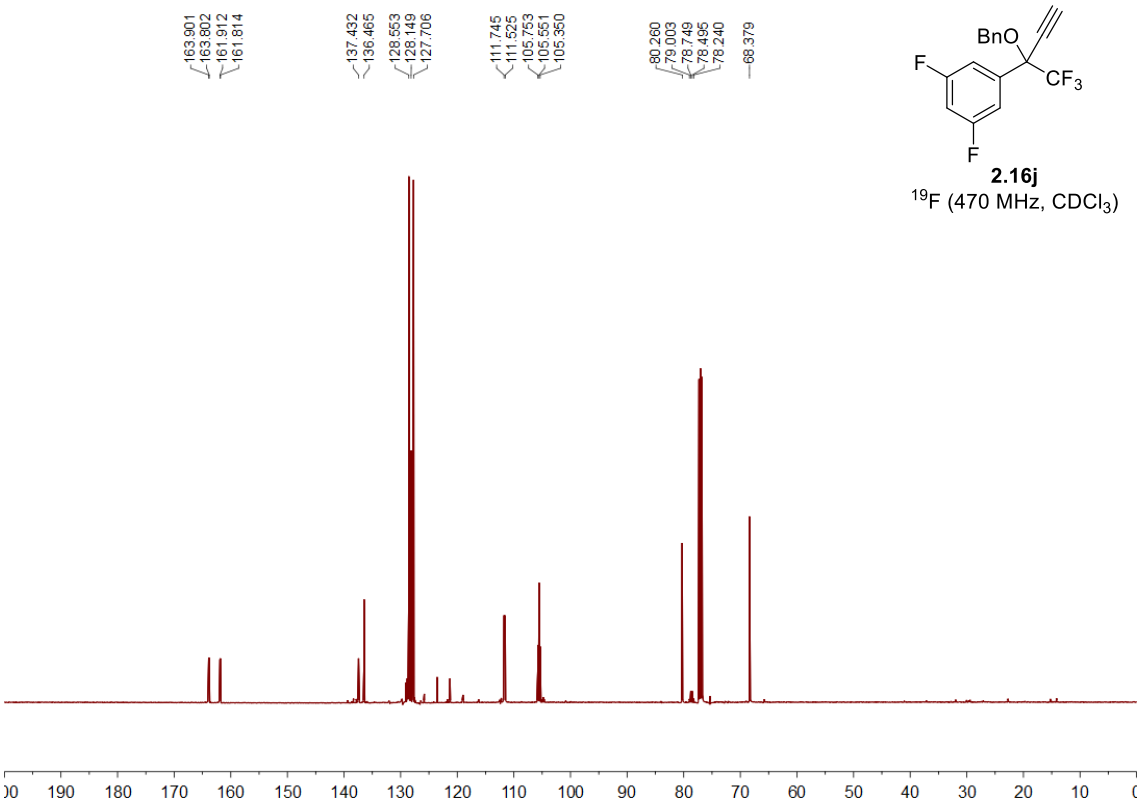
2.16j

^{1}H (500 MHz, $CDCl_3$)

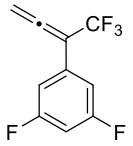


2.16j

^{13}C (125 MHz, $CDCl_3$)


163.901
163.802
161.912
161.814
137.432
136.465
128.553
128.149
127.706
111.745
111.525
105.753
105.551
105.350
80.260
79.003
78.749
78.495
78.240
68.379
BnO
F
CF3
F
2.16j
19F (470 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

1,3-difluoro-5-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (2.1j)



2.1j

Benzyl protected propargylic alcohol **2.16j** (326 mg, 1.0 mmol) was subjected to general procedure F. Upon flash column chromatography (SiO_2, pentane), the title compound **2.1j** (153 mg, 0.70 mmol) was obtained as a light yellow oil in 70% yield.

R_f = 0.48 (pentane).

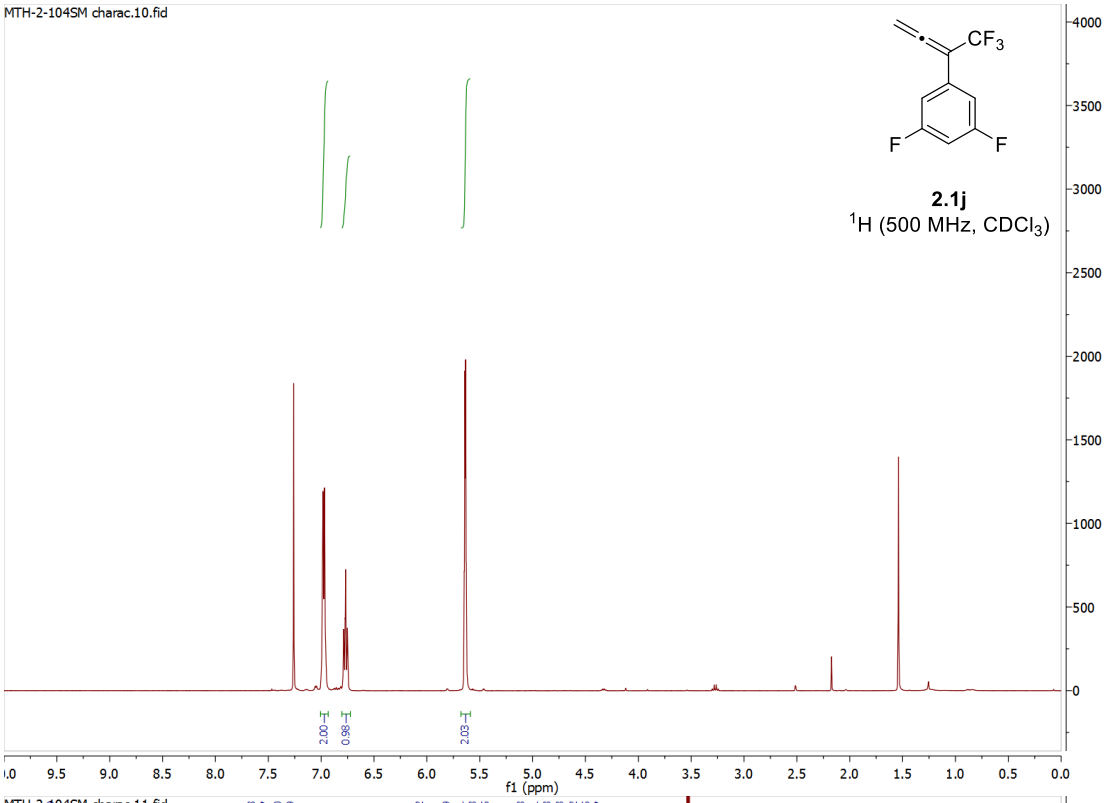
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.97 (br d, *J* = 7.2 Hz, 2H), 6.77 (tt, *J* = 1.9, 8.8 Hz, 1H), 5.64 (q, *J* = 3.3 Hz, 2H).

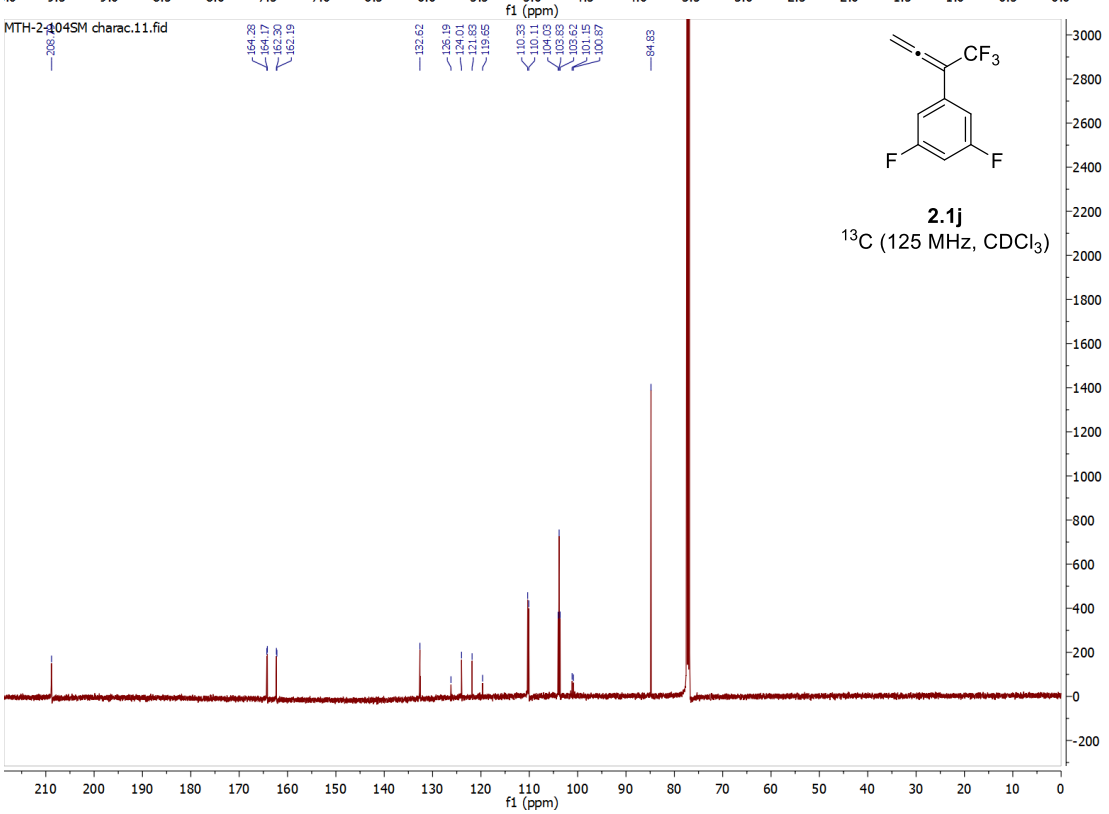
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.8 (q, *J* = 3.3 Hz), 163.2 (dd, *J* = 13.1, 249 Hz), 132.6 (t, *J* = 11.9 Hz), 122.9 (q, *J* = 271.4 Hz), 110.2 (m), 103.8 (t, *J* = 26.3 Hz), 101.0 (q, *J* = 34.1 Hz), 84.8.

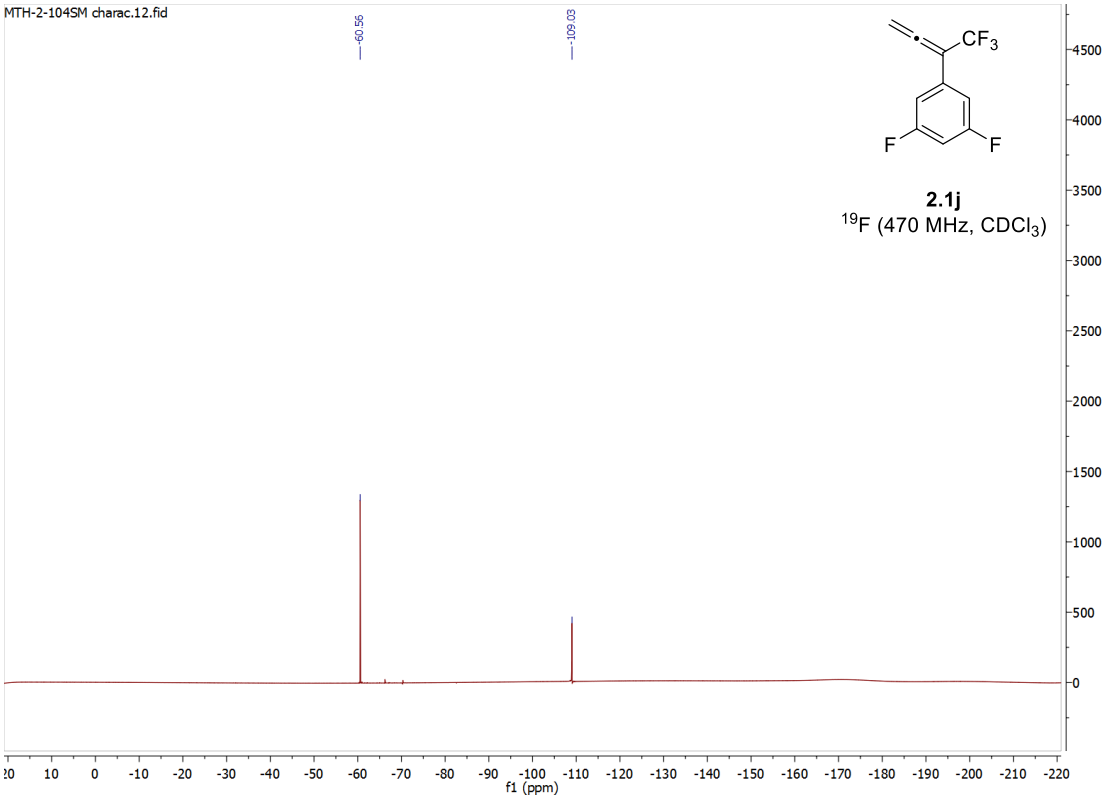
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.6 (t, *J* = 3.1 Hz), -101.9 (t, *J* = 8.3 Hz).

HRMS (CI+, *m/z*) for $C_{10}H_5F_5$: calcd. = 220.0305; found = 220.0311.

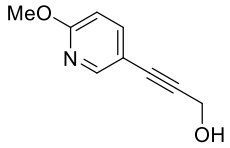
FTIR (neat): 2970, 2359, 1974, 1936, 1624, 1588, 1460, 1302, 1252, 1122, 986, 860, 716 cm^{-1}.


MTH-2-104SM charac.10.fid
CF3
F
F
2.1j
1H (500 MHz, CDCl3)
2.00
0.98
2.03
f1 (ppm)


MTH-2-104SM charac.11.fid
208.
164.28
164.17
162.30
162.19
132.62
126.19
124.01
121.83
119.65
110.33
110.11
104.03
103.83
103.62
101.15
100.87
84.83
CF3
F
F
2.1j
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-104SM charac.12.fid
-60.56
-109.03
CF3
F
F
2.1j
19F (470 MHz, CDCl3)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

3-(6-methoxypyridin-3-yl)prop-2-yn-1-ol (2.13k)



2.13k

2-Methoxy-5-bromopyridine (1.88 g, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:4 to 1:3 EtOAc/hexanes), the title compound **2.13k** (603 mg, 3.7 mmol) was obtained as a brown solid in 37% yield.

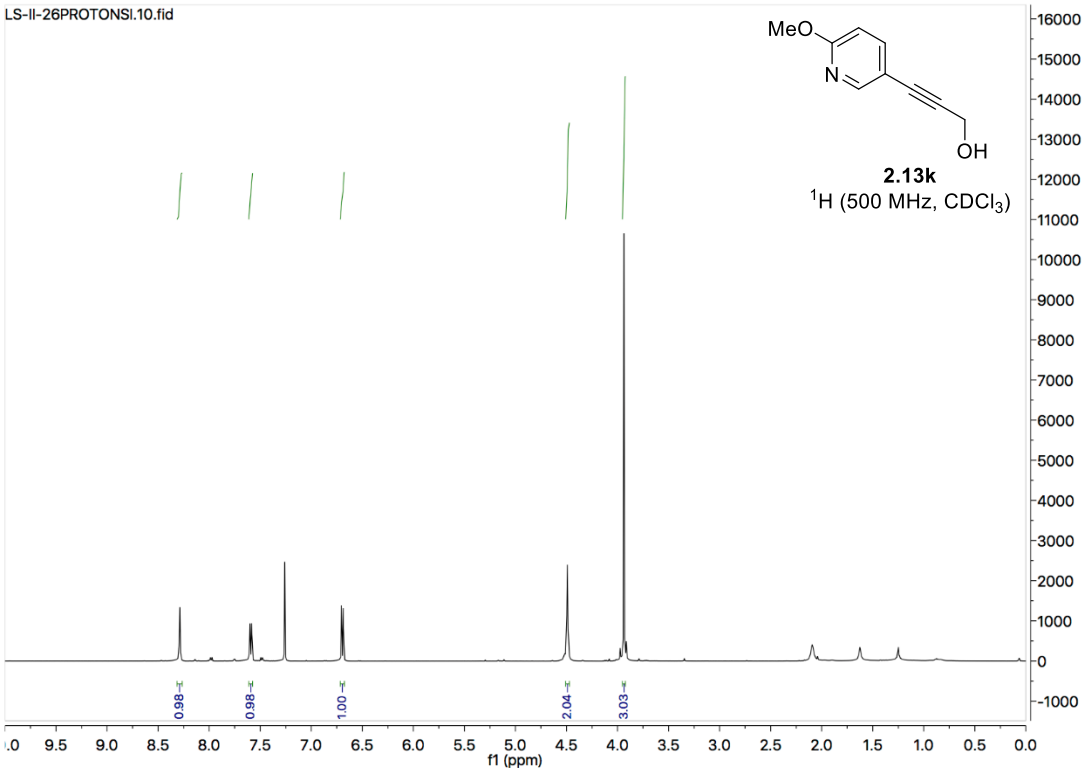
R_f = 0.21 (1:4 EtOAc/hexanes).

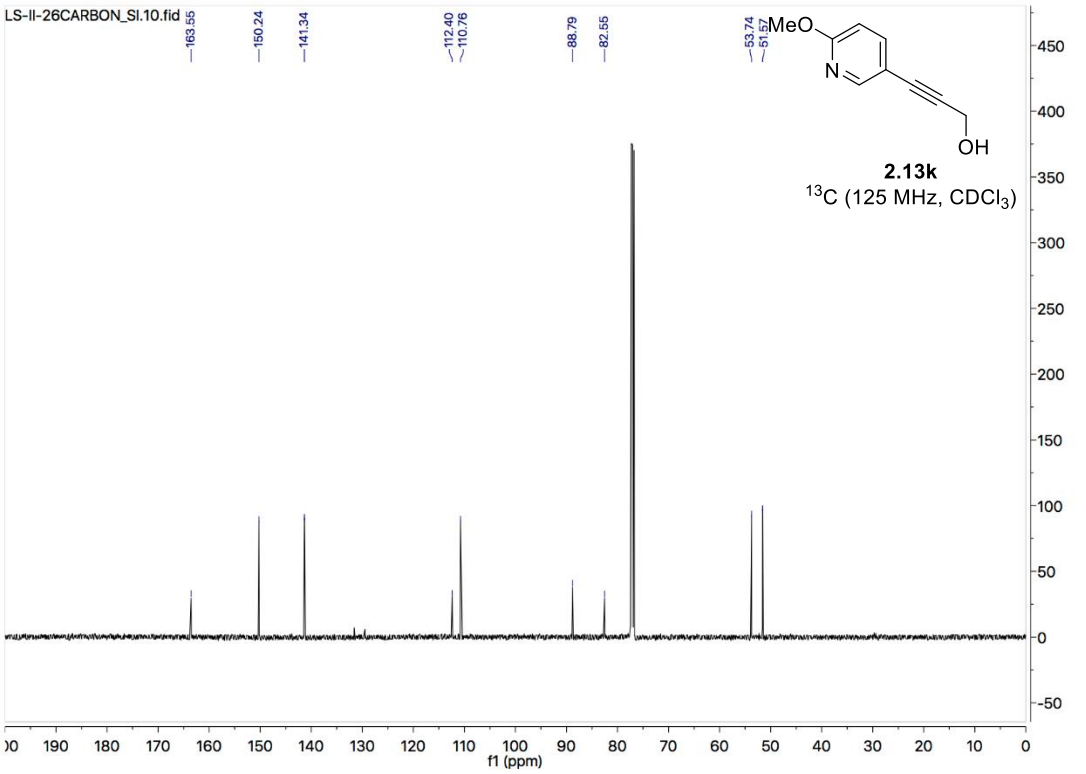
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 2.3, 8.6 Hz, 1H), 6.7 (d, J = 8.6 Hz, 1H), 4.49 (s, 2H), 3.94 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.6, 150.2, 141.3, 112.4, 110.8, 88.8, 82.6, 53.7, 51.6.

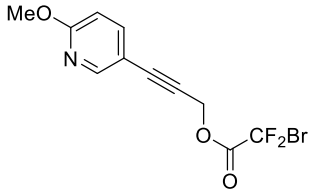
HRMS (H+, *m/z*) for $C_9H_9NO_2$: calcd. = 164.0706; found = 164.0703.

FTIR (neat): 3326, 2947, 1601, 1557, 1492, 1367, 1288, 1016, 831 cm^{-1}.


LS-II-26PROTONSI.10.fid
MeO
N
OH
2.13k
^{1}H (500 MHz, $CDCl_3$)
0.98
0.98
1.00
2.04
3.03
f1 (ppm)


LS-II-26CARBON_SI.10.fid
163.55
150.24
141.34
112.40
110.76
88.79
82.55
53.74
51.57
MeO
N
OH
2.13k
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

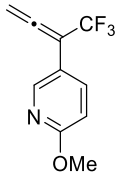
3-(6-methoxypyridin-3-yl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14k)



2.14k

Propargyl alcohol 6k (370 mg, 2.27 mmol) was subjected to general procedure B to furnish the title compound **2.14k**. This compound was unstable to silica gel so was filtered through a very short pad of silica gel and immediately used in the next reaction.

2-methoxy-5-(1,1,1-trifluorobuta-2,3-dien-2-yl)pyridine (2.1k)



2.1k

Crude progargyl bromodifluoroacetate **2.14k** was subjected to general procedure C. Upon flash column chromatography (SiO_2, 5:95 CH_2Cl_2/pentane), the title compound **2.1k** (236 mg, 1.1 mmol) was obtained as a colourless oil in 48% yield over two steps.

R_f = 0.24 (5:95 CH_2Cl_2/pentane).

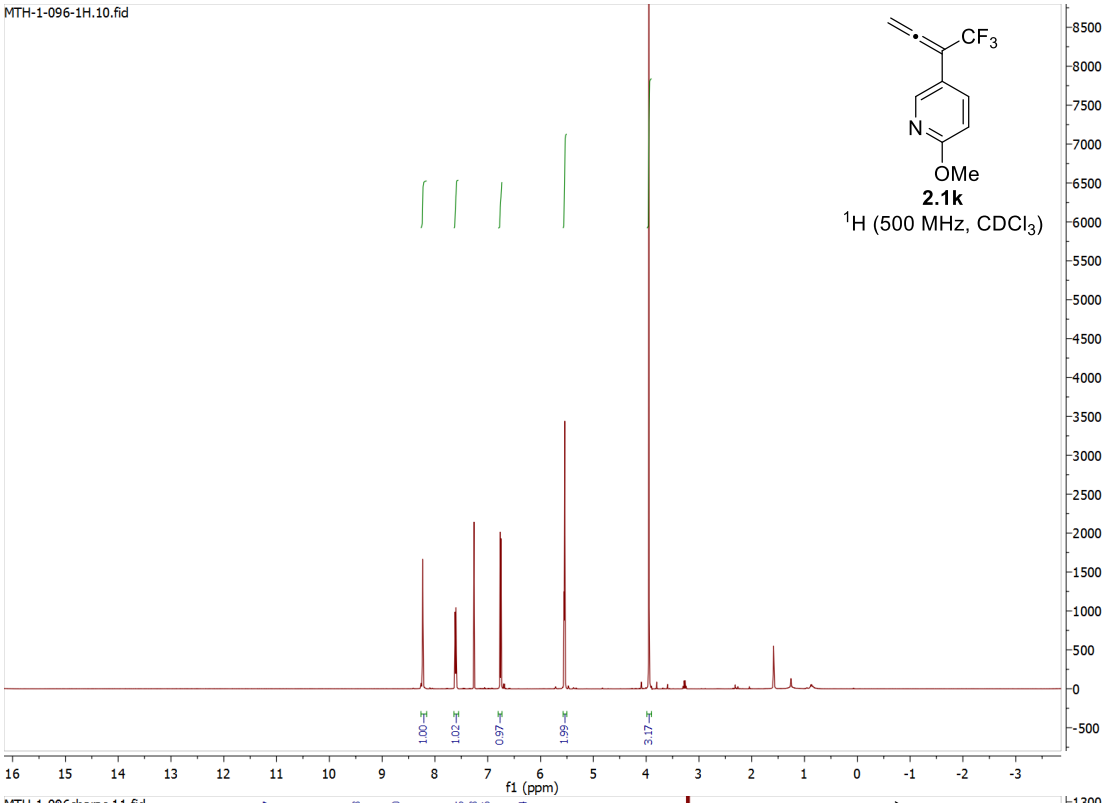
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (br s, 1H), 7.61 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 5.55 (q, *J* = 3.2 Hz, 2H), 3.95 (s, 3H).

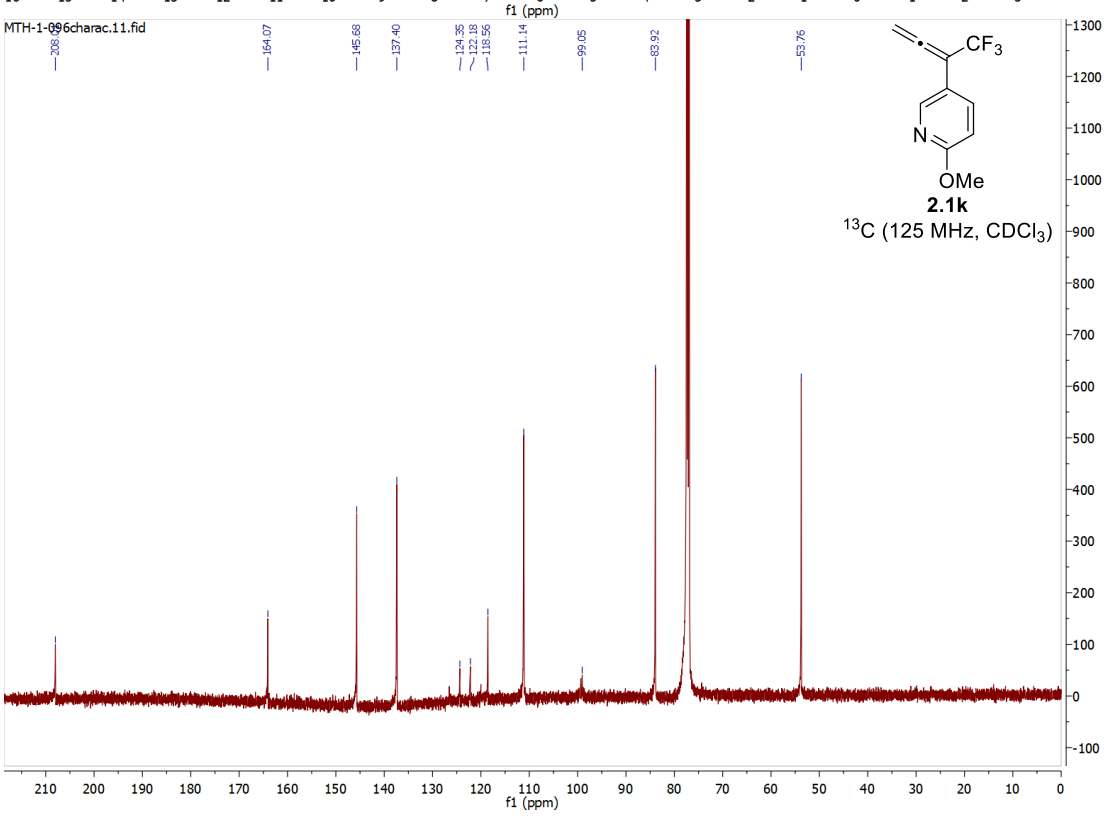
^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.9, 163.9, 145.5, 137.3, 123.0 (q, *J* = 273 Hz), 118.4, 111.0, 98.9 (q, *J* = 35 Hz), 83.8, 53.6.

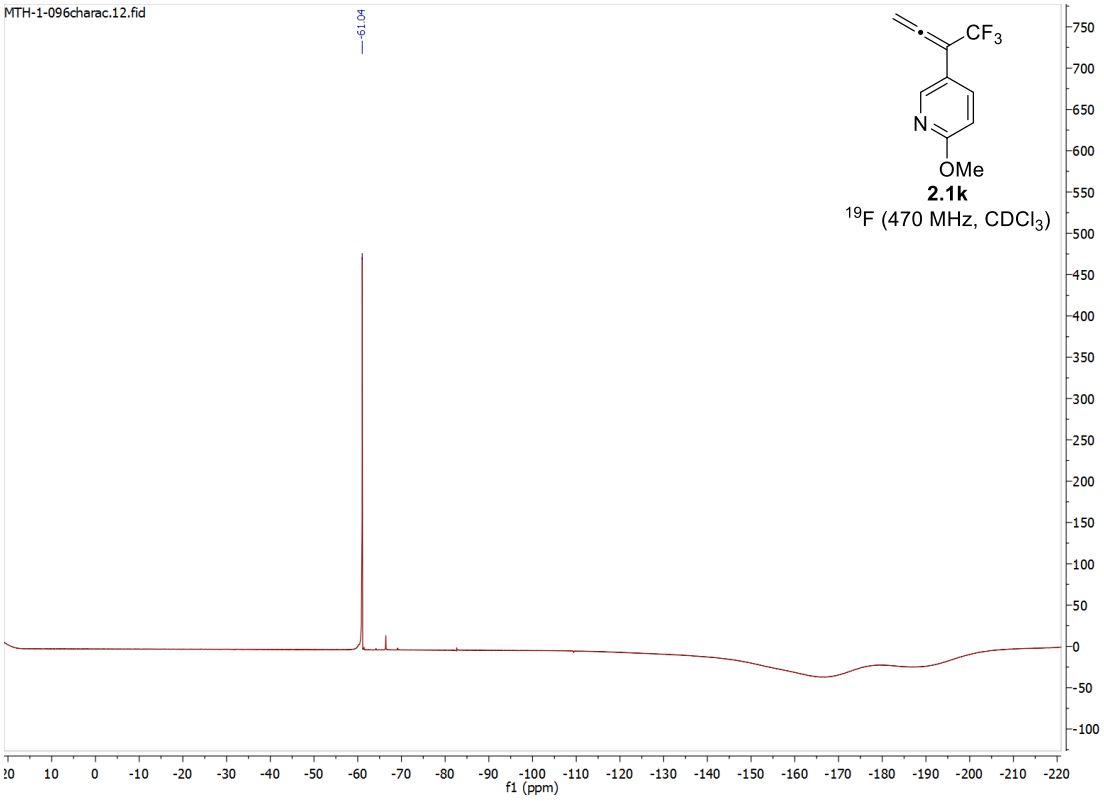
^{19}F NMR (470 MHz, $CDCl_3$) δ: -61.0.

HRMS (CI+, *m/z*) for $C_{10}H_8NOF_3$: calcd. = 215.0558; found = 215.0562.

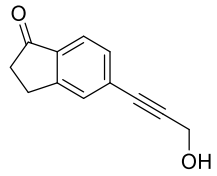
FTIR (neat): 2951, 1976, 1937, 1605, 1496, 1384, 1282, 1176, 1107, 1026, 933, 869, 831, 733 cm^{-1}.


MTH-1-096-1H.10.fid
CF3
N
OMe
2.1k
1H (500 MHz, CDCl3)
1.00
1.02
0.97
1.99
3.17
f1 (ppm)


MTH-1-096charac.11.fid
208.93
164.07
145.68
137.40
124.35
122.18
118.56
111.14
99.05
83.92
53.76
CF3
N
OMe
2.1k
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-1-096charac.12.fid
-61.04
CF3
N
OMe
2.1k
19F (470 MHz, CDCl3)
f1 (ppm)

5-(3-hydroxyprop-1-yn-1-yl)-2,3-dihydro-1H-inden-1-one (2.13l)



2.13l

5-bromo-1-indanone (4.43 g, 21 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:4 EtOAc/hexanes), the title compound **2.13l** (1.66 g, 8.94 mmol) was obtained as a brown solid in 43% yield.

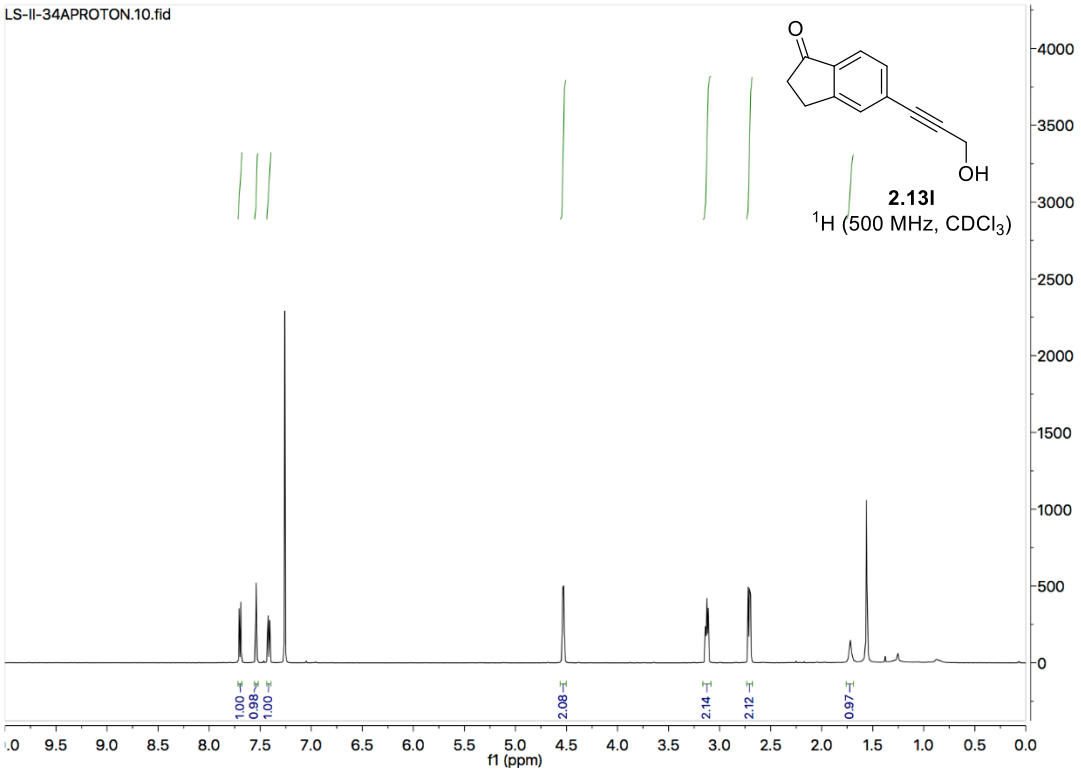
R_f = 0.13 (1:4 EtOAc/hexanes).

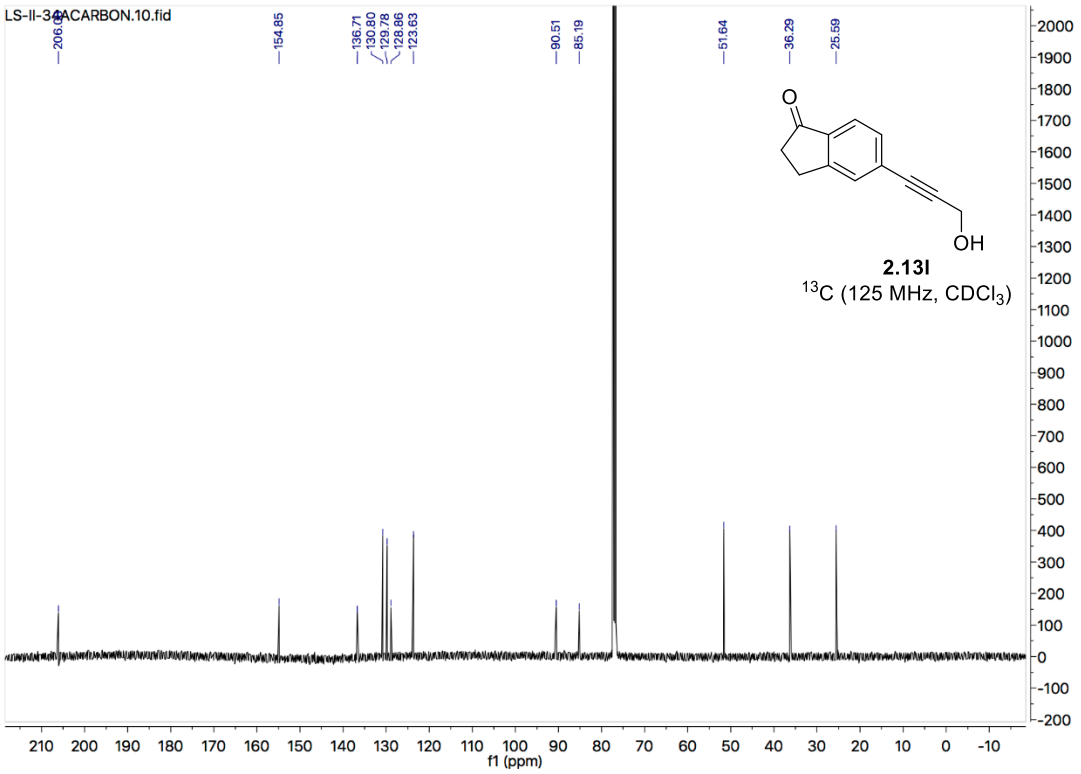
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 4.53 (br d, *J* = 4.2 Hz, 2H), 3.13 (t, *J* = 5.9 Hz, 2H), 2.71 (t, *J* = 6.0 Hz, 2H), 1.72 (br t, *J* = Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.1, 154.9, 136.7, 130.8, 129.8, 128.9, 123.6, 90.5, 85.2, 51.6, 36.3, 25.6.

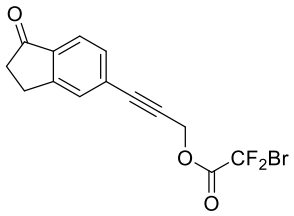
HRMS (CI+, *m/z*) for $C_{12}H_{10}O_2$: calcd. = 186.0681; found = 186.0683.

FTIR (neat): 3329, 2923, 2360, 2341, 1688, 1603, 1440, 1319, 1270, 1033 cm^{-1}.


LS-II-34APROTON.10.fid
O
OH
2.13l
^{1}H (500 MHz, $CDCl_3$)
1.00
0.98
1.00
2.08
2.14
2.12
0.97
f1 (ppm)


LS-II-34ACARBON.10.fid
206.69
154.85
136.71
130.80
129.78
128.86
123.63
90.51
85.19
51.64
36.29
25.59
O
OH
2.13l
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

3-(1-oxo-2,3-dihydro-1H-inden-5-yl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14l)



2.14l

Propargyl alcohol **2.13l** (1.66 g, 8.94 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:3 EtOAc/hexanes), the title compound **2.14l** (2.32 g, 6.76 mmol) was obtained as a light yellow oil in 76% yield.

R_f = 0.60 (1:3 EtOAc/hexanes).

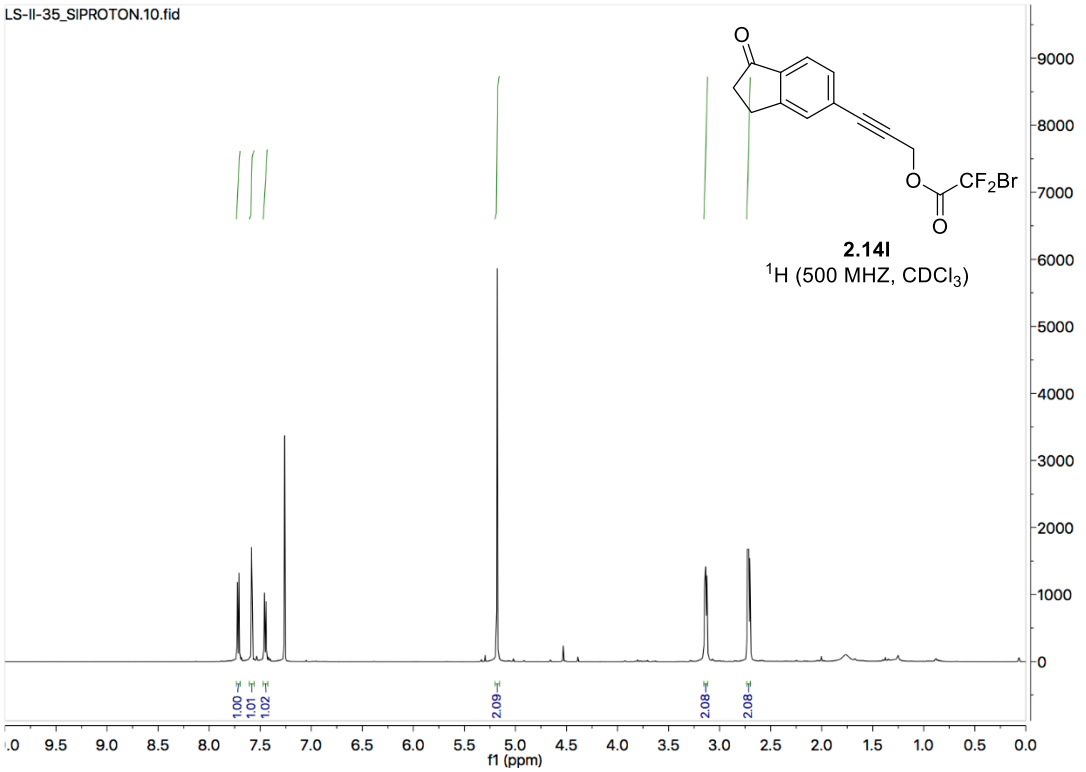
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 5.18 (s, 2H), 3.14 (t, *J* = 6.0 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H).

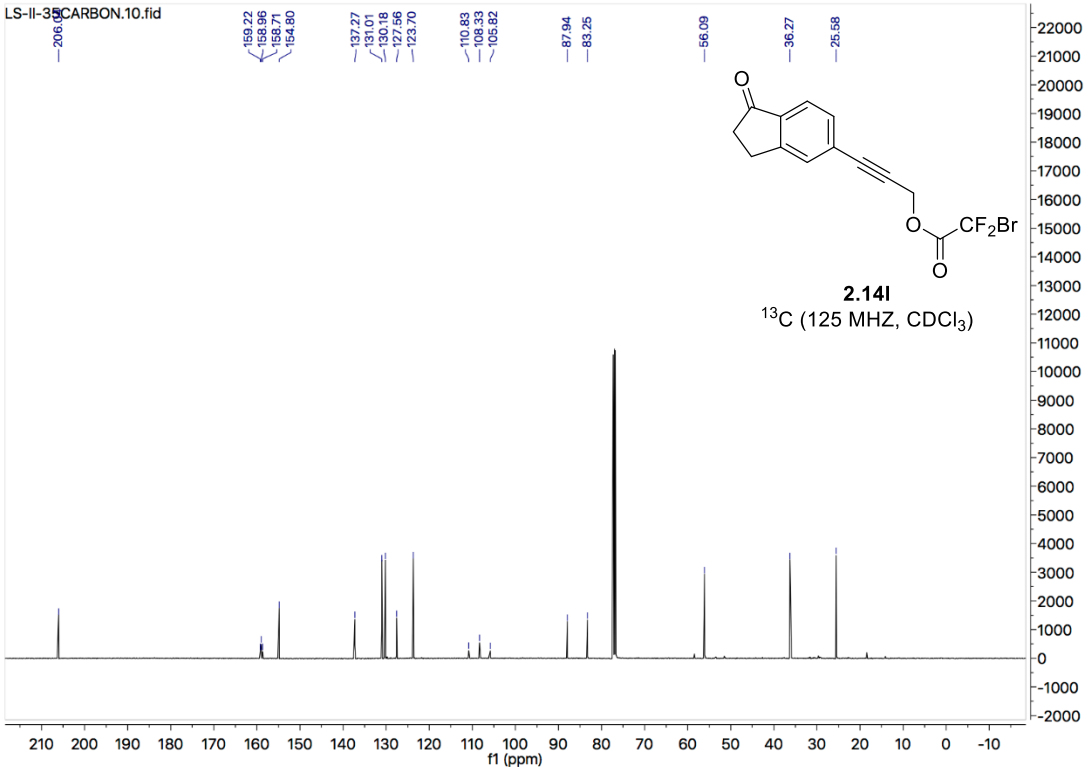
^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.1, 159.0 (t, *J* = 32.1 Hz), 154.8, 137.4, 131.0, 130.2, 127.6, 123.7, 108.3 (t, *J* = 313.3 Hz), 87.9, 83.4, 56.1, 36.3, 25.6.

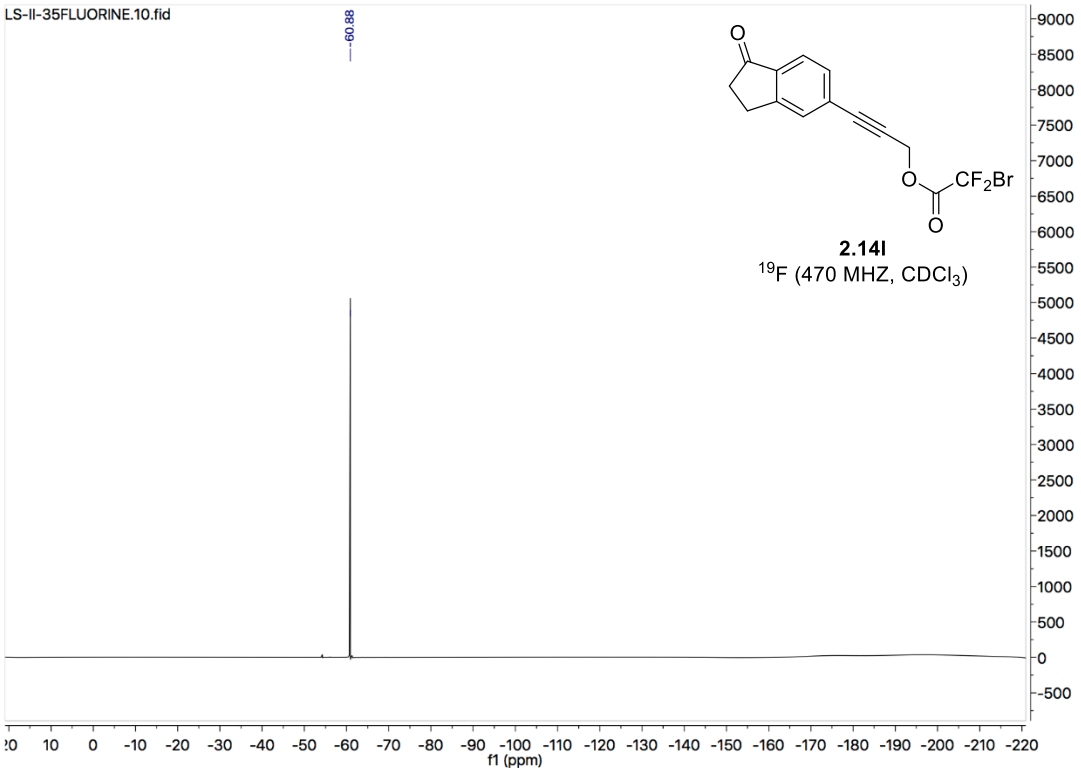
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.9.

HRMS (CI+, *m/z*) for $C_{14}H_9BrF_2O_3$ = 341.9703; found = 341.9683.

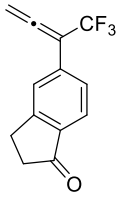
FTIR (neat): 2931, 2360, 2338, 1781, 1712, 1606, 1437, 1315, 1290, 1164, 1117, 697cm^{-1}.


LS-II-35_SIPROTON.10.fid
2.14l
1H (500 MHZ, CDCl3)
f1 (ppm)


LS-II-35_CARBON.10.fid
206.05
159.22
158.96
158.71
154.80
137.27
131.01
130.18
127.56
123.70
110.83
108.33
105.82
87.94
83.25
56.09
36.27
25.58
2.14l
13C (125 MHZ, CDCl3)
f1 (ppm)


LS-II-35FLUORINE.10.fid
-60.88
O
O
O
CF2Br
2.14l
19F (470 MHZ, CDCl3)
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

5-(1,1,1-trifluorobuta-2,3-dien-2-yl)-2,3-dihydro-1H-inden-1-one (2.1l)



2.1l

Progargyl bromodifluoroacetate **2.14l** (2.32 g, 6.76 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, 1:4 EtOAc/hexanes), the title compound **2.1l** (1.08 g, 4.55 mmol) was obtained as a pale yellow solid in 67% yield.

R_f = 0.23 (1:4 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 5.64 (q, *J* = 3.3 Hz, 2H), 3.16 (t, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H).

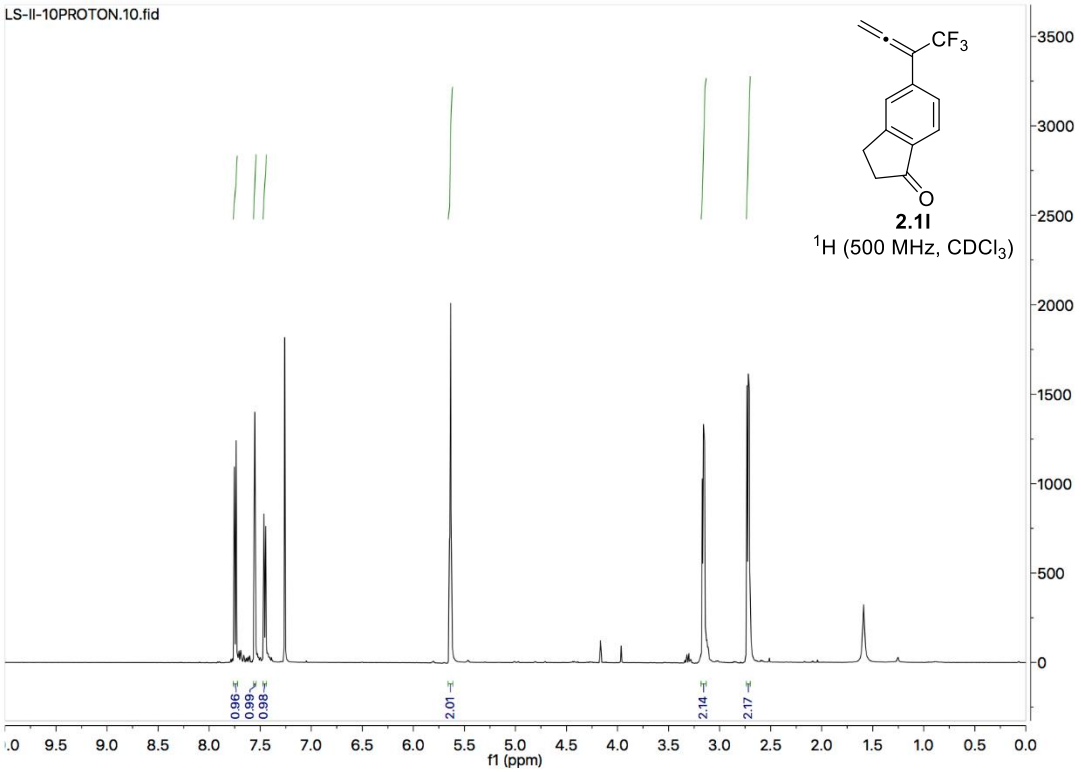
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.3 (q, J= 4.1 Hz), 206.2, 155.6, 136.7, 135.6, 126.5, 124.9, 124.0, 123.1 (q, *J* = 273.9 Hz), 101.7 (q, *J* = 34.3 Hz), 84.2, 36.4, 25.8.

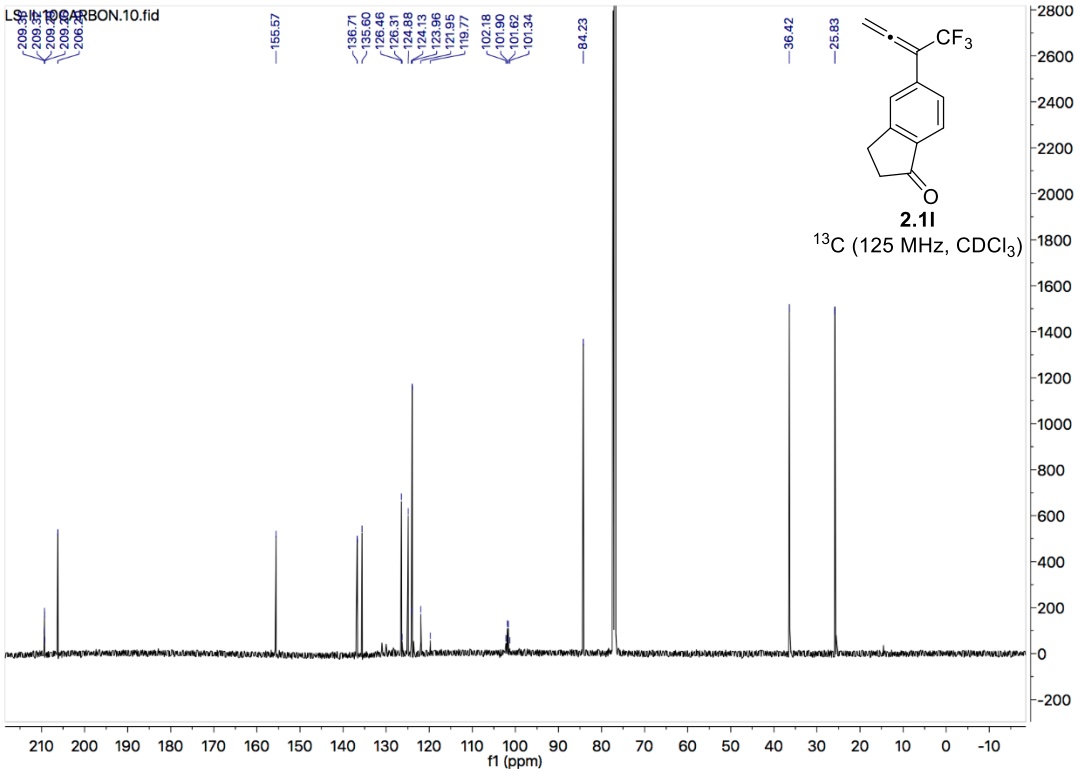
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.2.

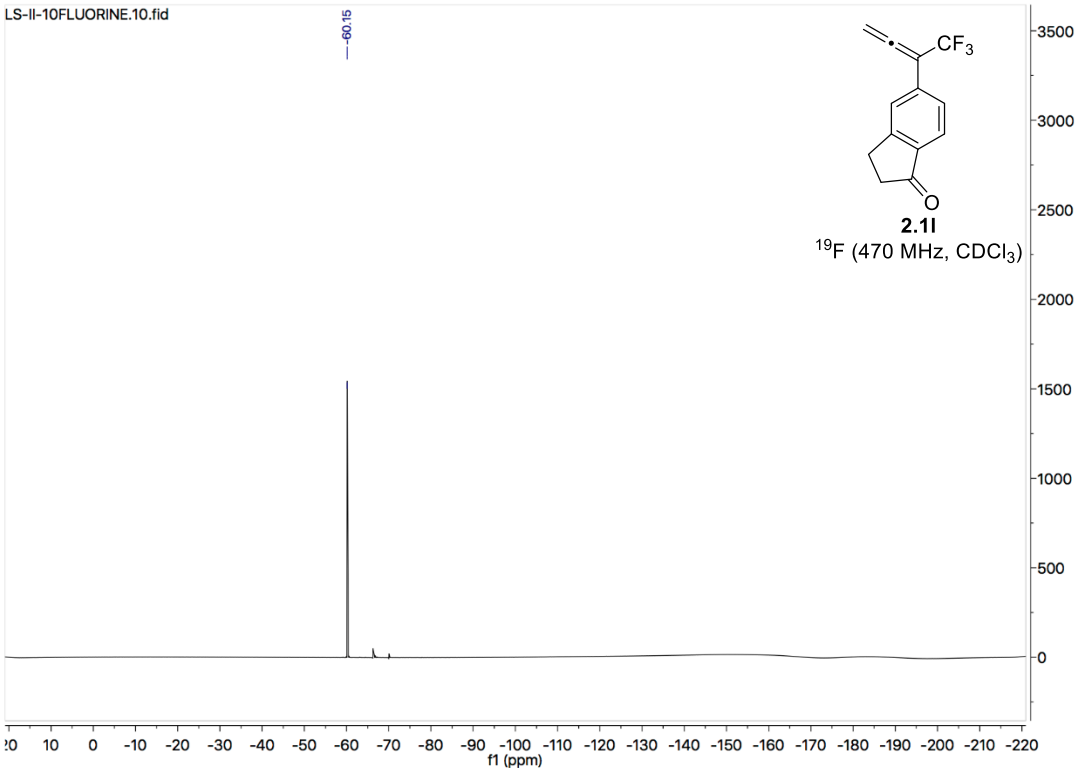
HRMS (CI+, *m/z*) for $C_{13}H_9F_3O$ = 238.0605; found = 238.0605.

FTIR (neat): 3051, 2963, 1965, 1930, 1698, 1605, 1289, 1124, 1105, 1093, 725 cm^{-1}.

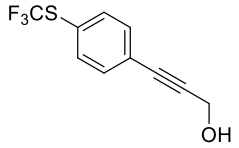
Melting Point: 89-90 °C


LS-II-10PROTON.10.fid
CF3
O
2.1l
1H (500 MHz, CDCl3)
0.96
0.99
0.98
2.01
2.14
2.17
f1 (ppm)


LS-II-10CARBON.10.fid
155.57
136.71
135.60
126.46
126.31
124.88
124.13
123.96
121.95
119.77
102.18
101.90
101.62
101.34
84.23
36.42
25.83
CF3
O
2.1l
13C (125 MHz, CDCl3)
f1 (ppm)


LS-II-10FLUORINE.10.fid
-60.15
CF3
O
2.1l
19F (470 MHz, CDCl3)
3500
3000
2500
2000
1500
1000
500
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

3-(4-((trifluoromethyl)thio)phenyl)prop-2-yn-1-ol (2.13m)



2.13m

4-(trifluoromethylthio)bromobenzene (2.57 g, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:4 EtOAc/hexanes), the title compound **2.13m** (1.64 g, 7.1 mmol) was obtained as a white solid in 71% yield.

R_f = 0.21 (1:3 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 4.51 (d, *J* = 6.1 Hz, 2H), 1.67 (t, *J* = 6.1 Hz, 1H, O*H*).

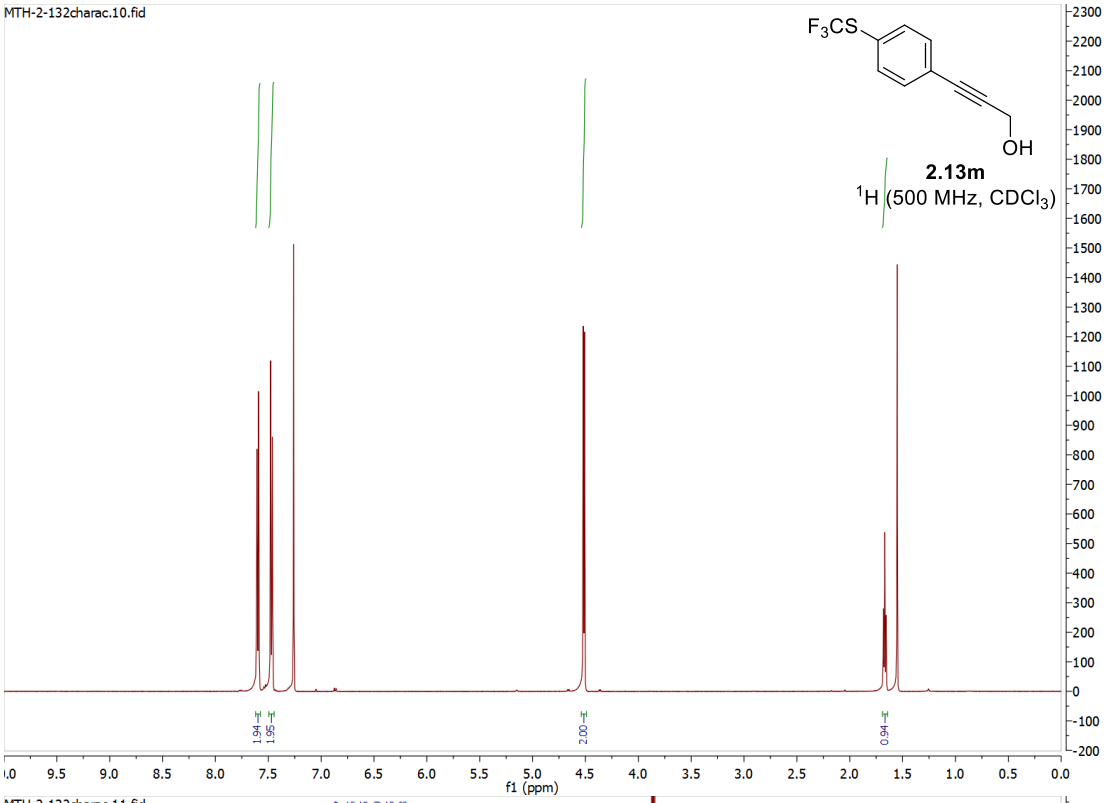
^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.2, 132.7, 129.6 (q, *J* = 318 Hz), 125.6, 124.8, 90.0, 84.6, 51.8.

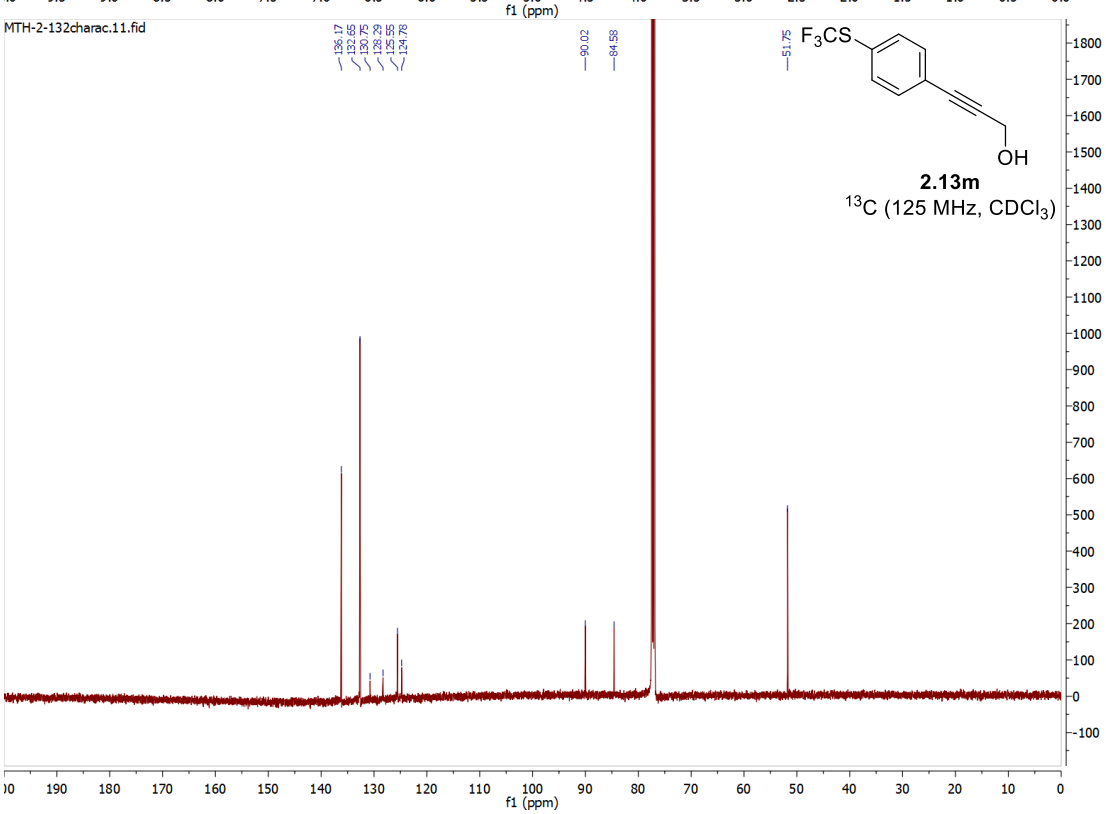
^{19}F NMR (470 MHz, $CDCl_3$) δ: -42.5.

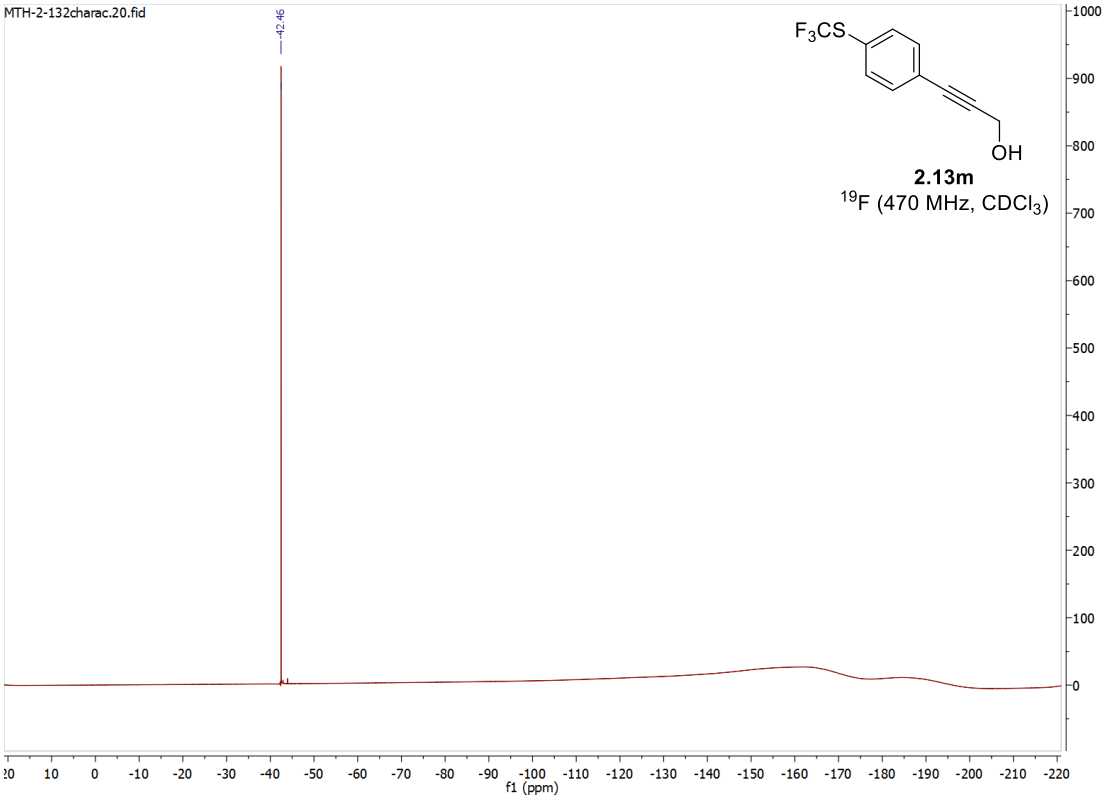
HRMS (CI+, *m/z*) for $C_{10}H_6OSF_3$: calcd. = 231.0091; found = 231.0084.

FTIR (neat): 3317, 2951, 1591, 1484, 1397, 1262, 1114, 1084, 1017, 833, 755 cm^{-1}.

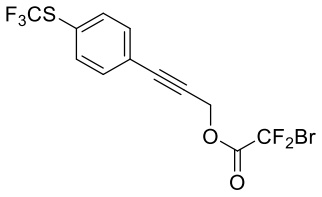
MP = 78-79 °C


MTH-2-132charac.10.fid
F3CS
OH
2.13m
1H (500 MHz, CDCl3)
1.94
1.95
2.00
0.94
f1 (ppm)


MTH-2-132charac.11.fid
136.17
133.65
130.75
128.29
125.55
124.78
90.02
84.58
51.75
F3CS
OH
2.13m
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-132charac.20.fid
-42.46
F3CS
OH
2.13m
19F (470 MHz, CDCl3)
1000
900
800
700
600
500
400
300
200
100
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

3-(4-((trifluoromethyl)thio)phenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14m)



2.14m

Propargyl alcohol **2.13m** (1.40 g, 6.5 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:20 EtOAc/hexanes), the title compound **2.14m** (1.70 g, 4.4 mmol) was obtained as a light yellow oil in 58% yield.

R_f = 0.67 (1:5 EtOAc/hexanes).

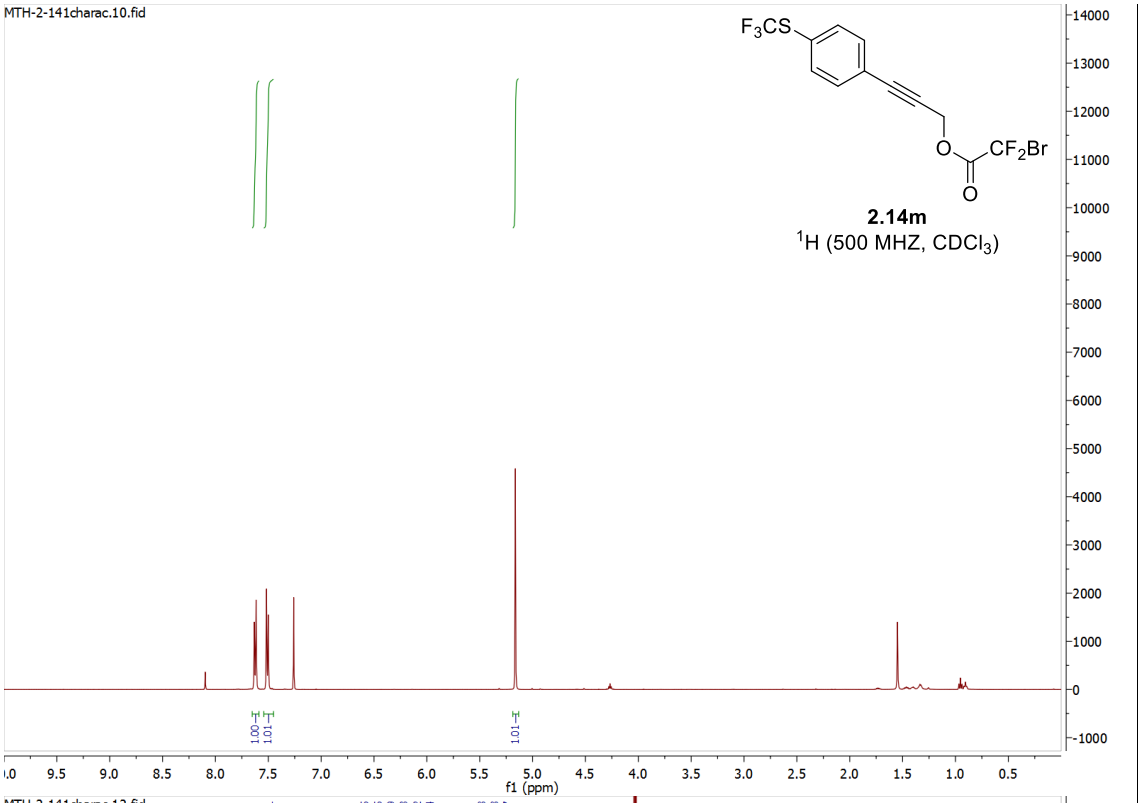
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 2H).

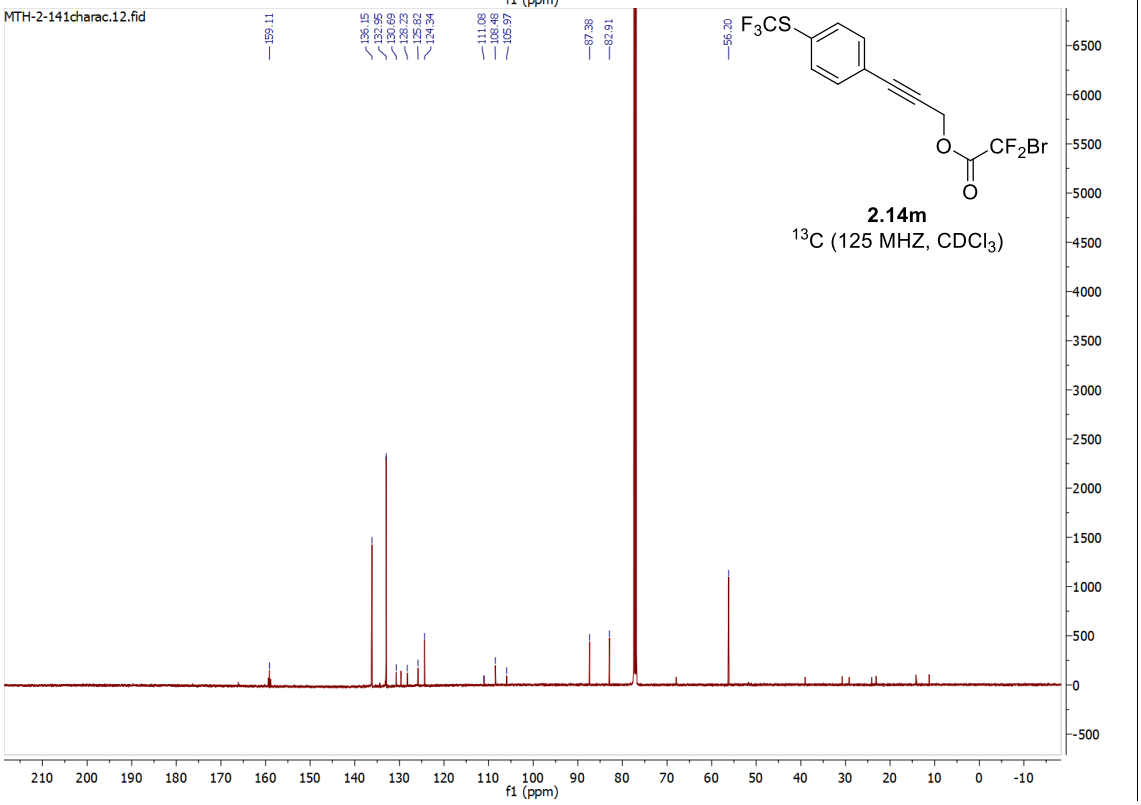
^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.1 (t, *J* = 32.1 Hz), 136.2, 133.0, 129.4 (q, *J* = 312 Hz), 125.8 (q, *J* = 2.2 Hz), 124.3, 108.5 (t, *J* = 314 Hz), 87.4, 82.9, 56.2.

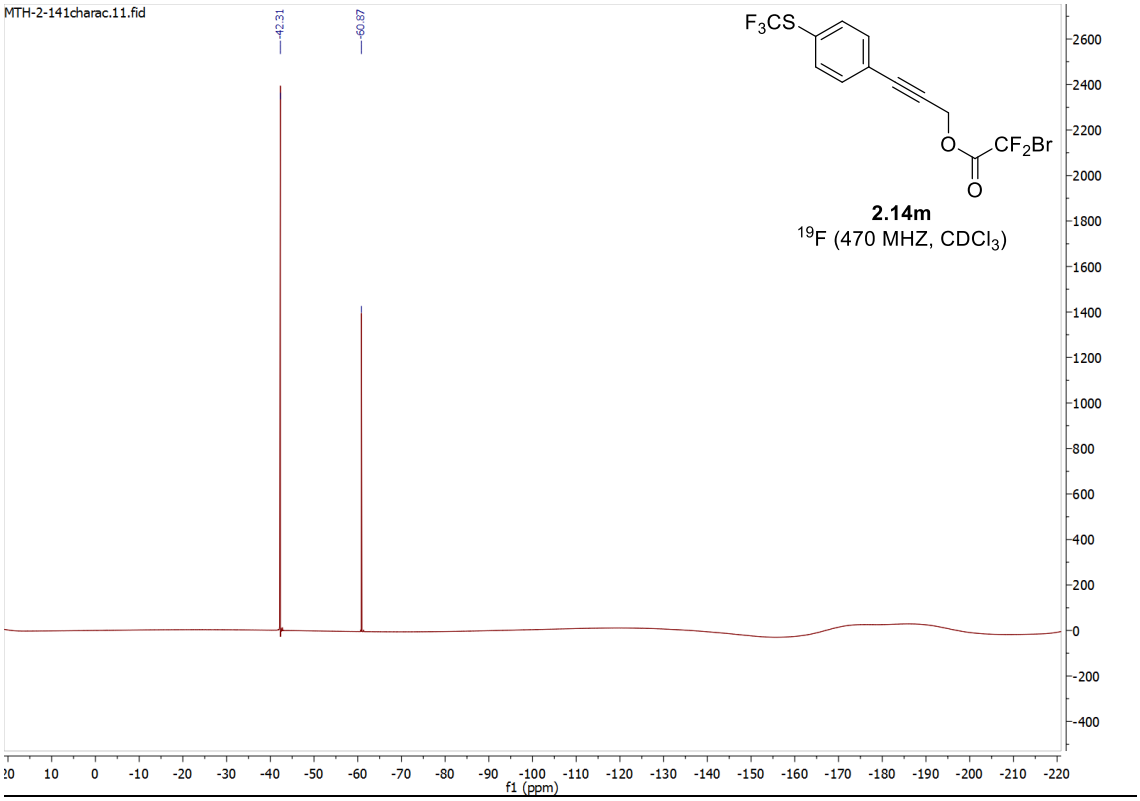
^{19}F NMR (470 MHz, $CDCl_3$) δ: -42.3, -60.9.

HRMS (CI+, *m/z*) for $C_{12}H_6BrF_5O_2S$ = 387.9192 ; found = 387.9189.

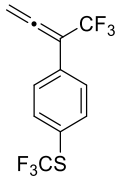
FTIR (neat): 2967, 2844, 1781, 1486, 1289, 1083, 1032, 1017, 947, 833 cm^{-1}.


MTH-2-141charac.10.fid
F3CS
O
CF2Br
O
2.14m
1H (500 MHZ, CDCl3)
1.00
1.01
1.01
f1 (ppm)


MTH-2-141charac.12.fid
159.11
136.15
132.95
130.69
128.23
125.82
124.34
111.08
108.48
105.97
87.38
82.91
56.20
F3CS
O
CF2Br
O
2.14m
13C (125 MHZ, CDCl3)
f1 (ppm)


MTH-2-141charac.11.fid
-42.31
-60.87
F3CS
O
CF2Br
O
2.14m
19F (470 MHZ, CDCl3)
f1 (ppm)

(4-(1,1,1-trifluorobuta-2,3-dien-2-yl)phenyl)(trifluoromethyl)sulfane (2.1m)



2.1m

Progargyl bromodifluoroacetate **2.14m** (1.70 g, 4.4 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, hexanes), the title compound **2.1m** (0.72 g, 2.5 mmol) was obtained as a pale yellow solid in 58% yield.

R_f = 0.71 (1:10 CH_2Cl_2/hexanes).

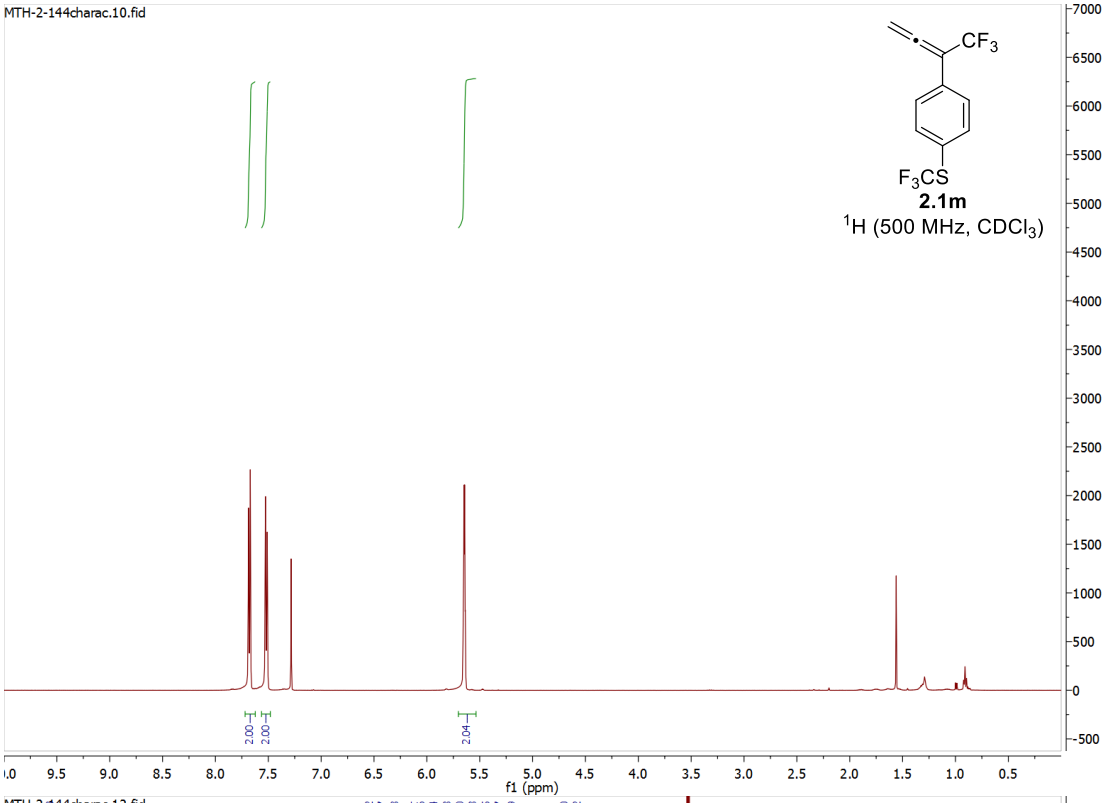
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 5.65 (q, *J* = 3.2 Hz, 2H).

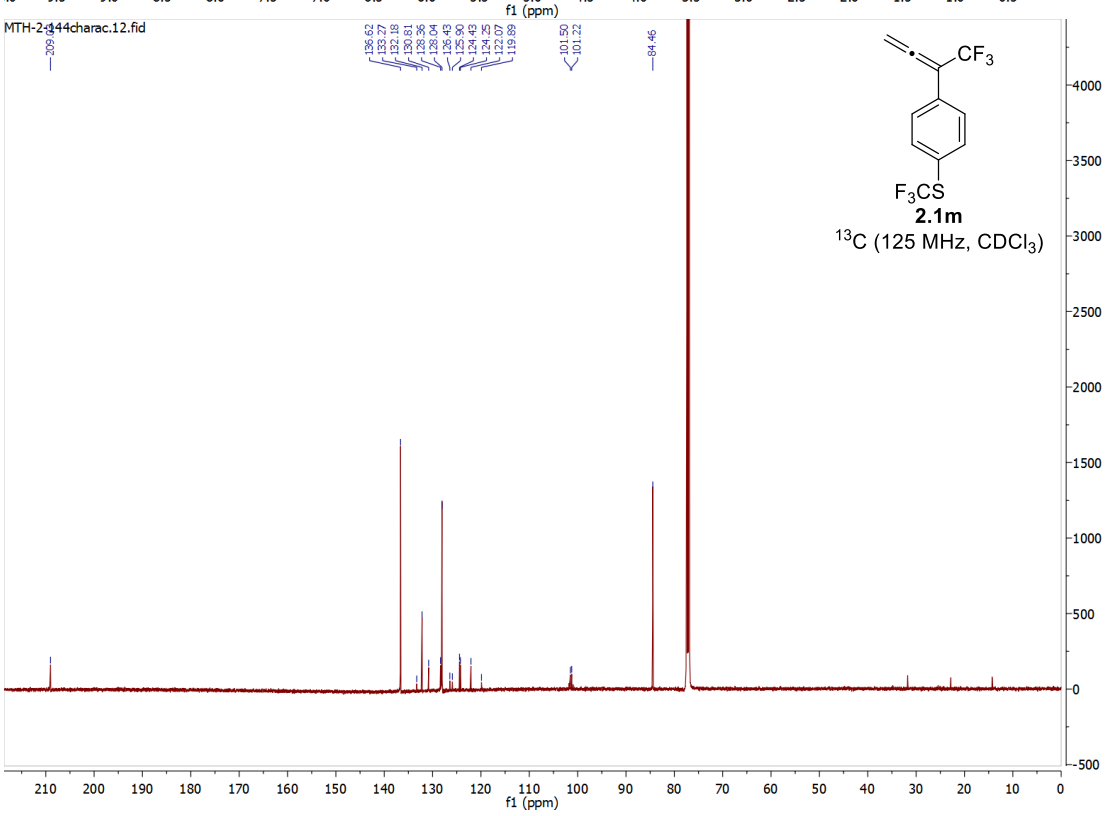
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.0 (q, *J* = 5.2 Hz), 136.6, 132.2, 129.5 (q, *J* = 310 Hz), 128.0, 124.4, 123.2 (q, *J* = 272 Hz), 101.3 (q, *J*= 44.5 Hz), 84.5.

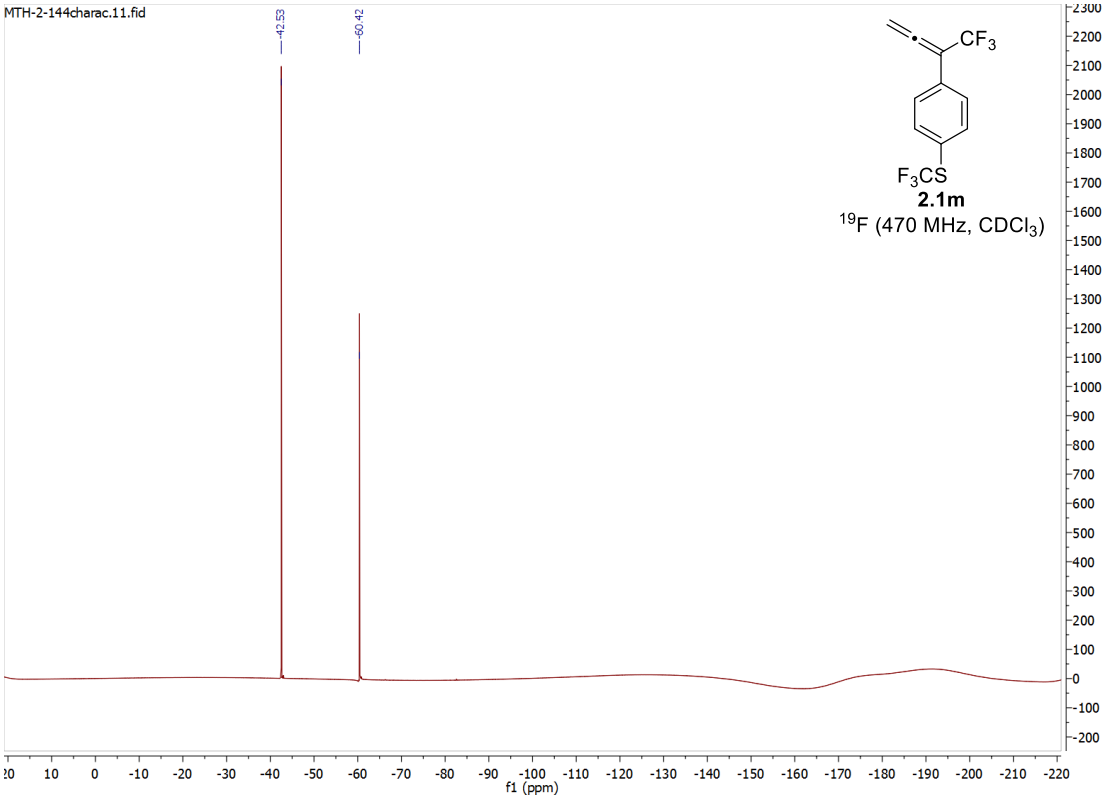
^{19}F NMR (470 MHz, $CDCl_3$) δ: -42.5, -60.4.

HRMS (CI+, *m/z*) for $C_{11}H_6F_6S$ = 284.0094; found = 384.0101.

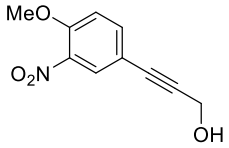
FTIR (neat): 2981, 1972, 1595, 1497, 1308, 1291, 1117, 1018, 937, 868, 836 cm^{-1}.


MTH-2-144charac.10.fid
CF3
F3CS
2.1m
1H (500 MHz, CDCl3)
2.00
2.00
2.04
f1 (ppm)


MTH-2-144charac.12.fid
209.14
136.62
133.27
132.18
130.51
128.36
128.04
126.43
125.90
124.43
124.25
122.07
119.89
101.50
101.22
84.46
CF3
F3CS
2.1m
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-144charac.11.fid
-42.53
-60.42
CF3
F3CS
2.1m
19F (470 MHz, CDCl3)
f1 (ppm)

3-(4-methoxy-3-nitrophenyl)prop-2-yn-1-ol (2.13n)



2.13n

4-iodo-2-nitroanisole (2.79 g, 10 mmol) was subjected to general procedure A. Upon flash column chromatography (SiO_2, 1:2 EtOAc/hexanes), the title compound **2.13n** (1.71 g, 8.3 mmol) was obtained as a yellow solid in 83% yield.

R_f = 0.09 (1:4 EtOAc/hexanes).

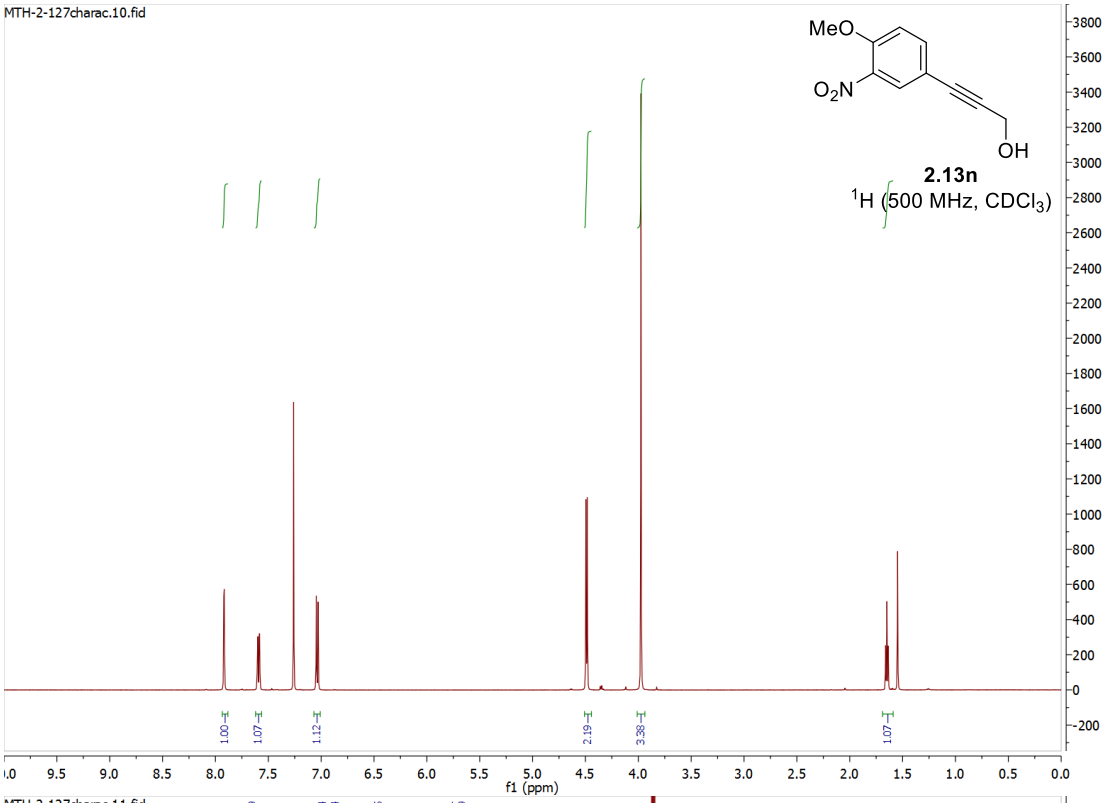
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 2.0, 8.7 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.97 (s, 3H), 1.65 (t, *J* = 5.9 Hz, 1H, O*H*).

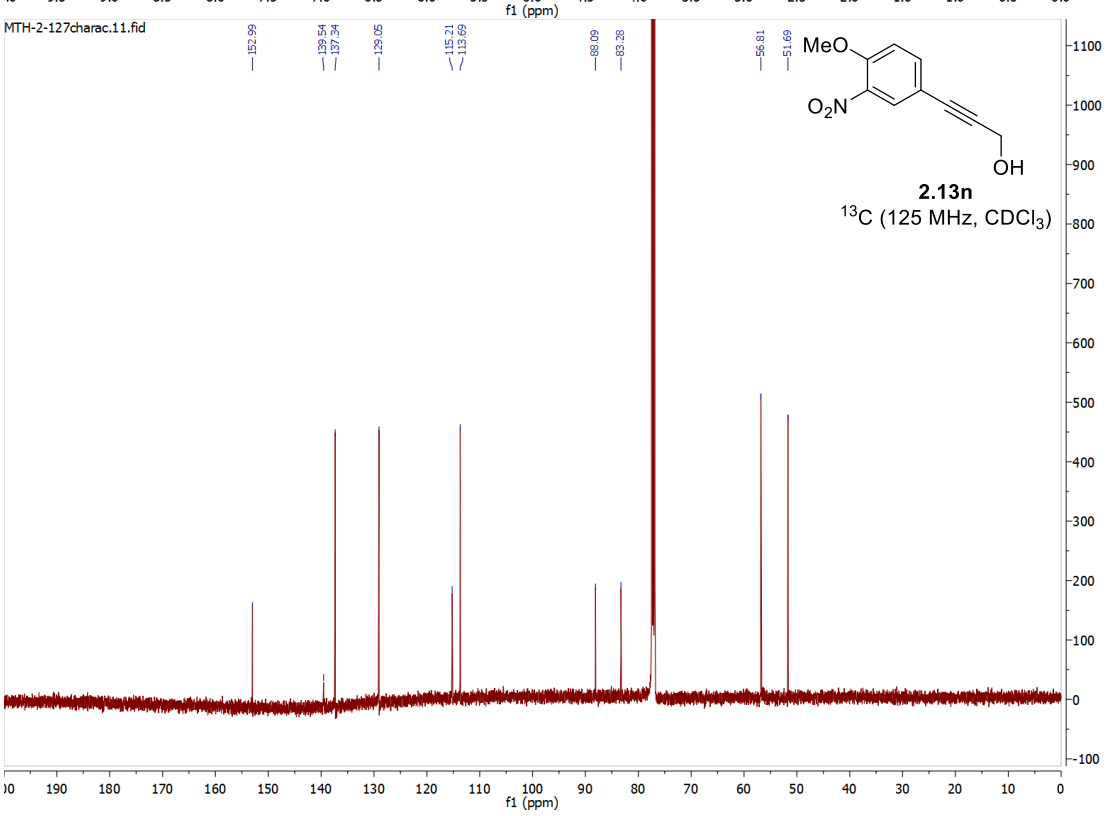
^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.0, 139.4, 137.3, 129.1, 115.2, 113.7, 88.1, 83.3, 56.8, 51.7.

HRMS (CI+, *m/z*) for $C_{10}H_9NO_4$: calcd. = 207.0532; found = 207.0531.

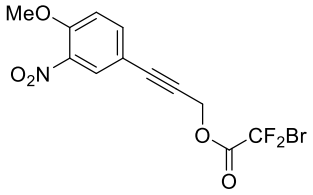
FTIR (neat): 3367, 2942, 1618, 1529, 1348, 1273, 1032, 878, 822 cm^{-1}.

MP = 94-95 °C


MTH-2-127charac.10.fid
MeO
O2N
OH
2.13n
1H (500 MHz, CDCl3)
1.00
1.07
1.12
2.19
3.38
1.07
f1 (ppm)


MTH-2-127charac.11.fid
152.99
139.54
137.34
129.05
115.21
113.69
88.09
83.28
56.81
51.69
MeO
O2N
OH
2.13n
13C (125 MHz, CDCl3)
f1 (ppm)

3-(4-methoxy-3-nitrophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate (2.14n)



2.14n

Propargyl alcohol **2.13n** (1.24 g, 6.0 mmol) was subjected to general procedure B. Upon flash column chromatography (SiO_2, 1:10 EtOAc/hexanes), the title compound **2.14n** (1.0 g, 2.75 mmol) was obtained as a light yellow oil in 46% yield.

R_f = 0.20 (1:10 EtOAc/hexanes).

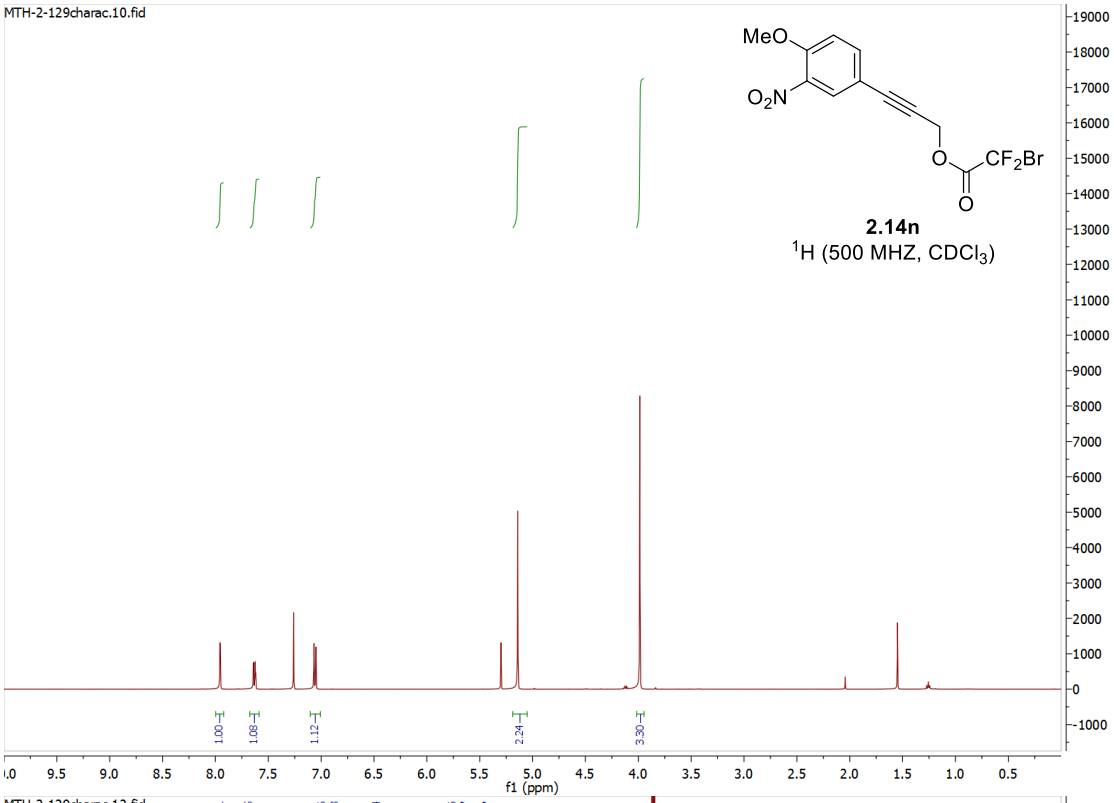
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 2.1 Hz, 1H), 7.63 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 5.14 (s, 2H), 3.99 (s, 3H).

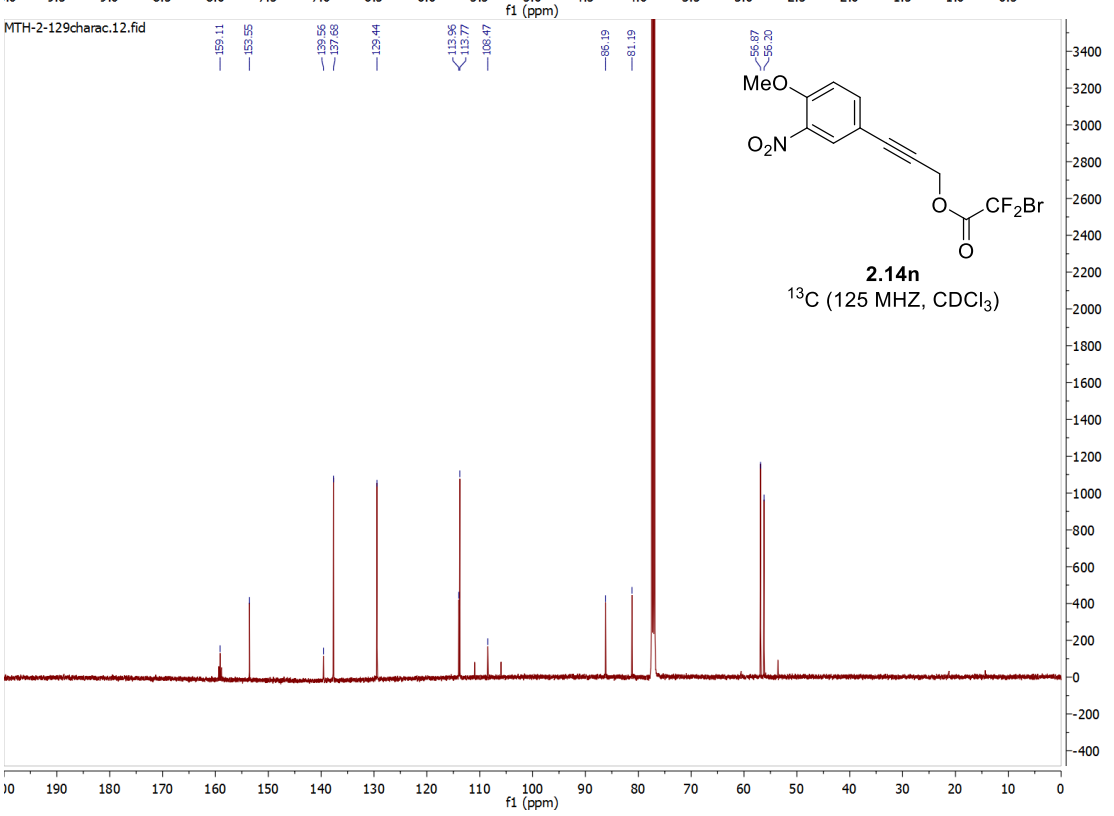
^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.1 (t, *J* = 31.6 Hz), 153.6, 139.6, 137.7, 129.4, 114.0, 113.8, 108.5 (t, *J* = 313.5 Hz), 86.2, 81.2, 56.9, 56.2.

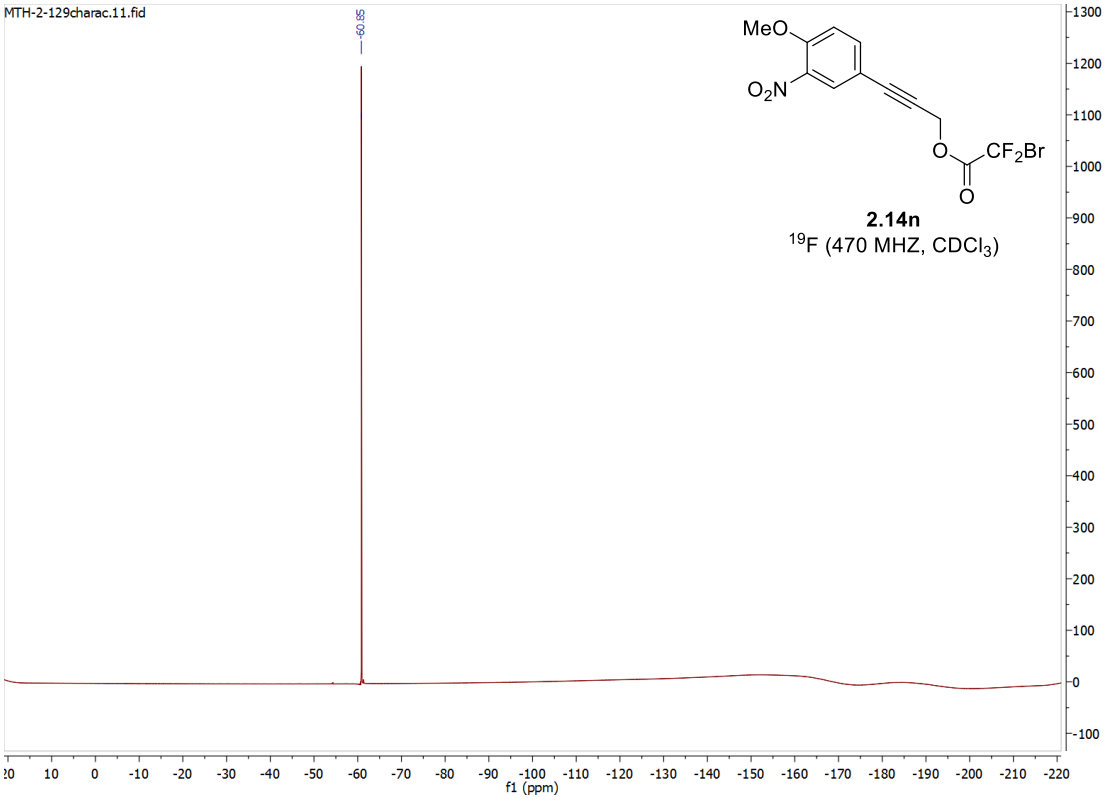
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.9.

HRMS (CI+, *m/z*) for $C_{14}H_9BrF_2O_3$ = product not observed. MS peak for starting material 6n was observed instead.

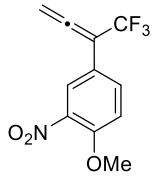
FTIR (neat): 2949, 2235, 1780, 1617, 1532, 1550, 1352, 1281, 1119, 1017, 951 cm^{-1}.


MTH-2-129charac.10.fid
MeO
O2N
O
CF2Br
O
2.14n
1H (500 MHZ, CDCl3)
1.00
1.08
1.12
2.24
3.30
f1 (ppm)


MTH-2-129charac.12.fid
159.11
153.55
139.56
137.68
129.44
113.96
113.77
108.47
86.19
81.19
56.87
56.20
MeO
O2N
O
CF2Br
O
2.14n
13C (125 MHZ, CDCl3)
f1 (ppm)


MTH-2-129charac.11.fid
-60.85
MeO
O2N
O
CF2Br
O
2.14n
19F (470 MHZ, CDCl3)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

1-methoxy-2-nitro-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (2.1n)



2.1n

Progargyl bromodifluoroacetate **2.14n** (1.0 g, 2.27 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, 1:10 EtOAc/hexanes), the title compound **2.1n** (372 mg, 1.43 mmol) was obtained as a pale yellow solid in 63% yield.

R_f = 0.24 (1:10 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 2.2, 9.7 Hz, 1H), 7.10 (d, *J* = 9.7 Hz, 1H), 5.63 (q, *J* = 3.3 Hz, 2H), 3.98 (s, 3H).

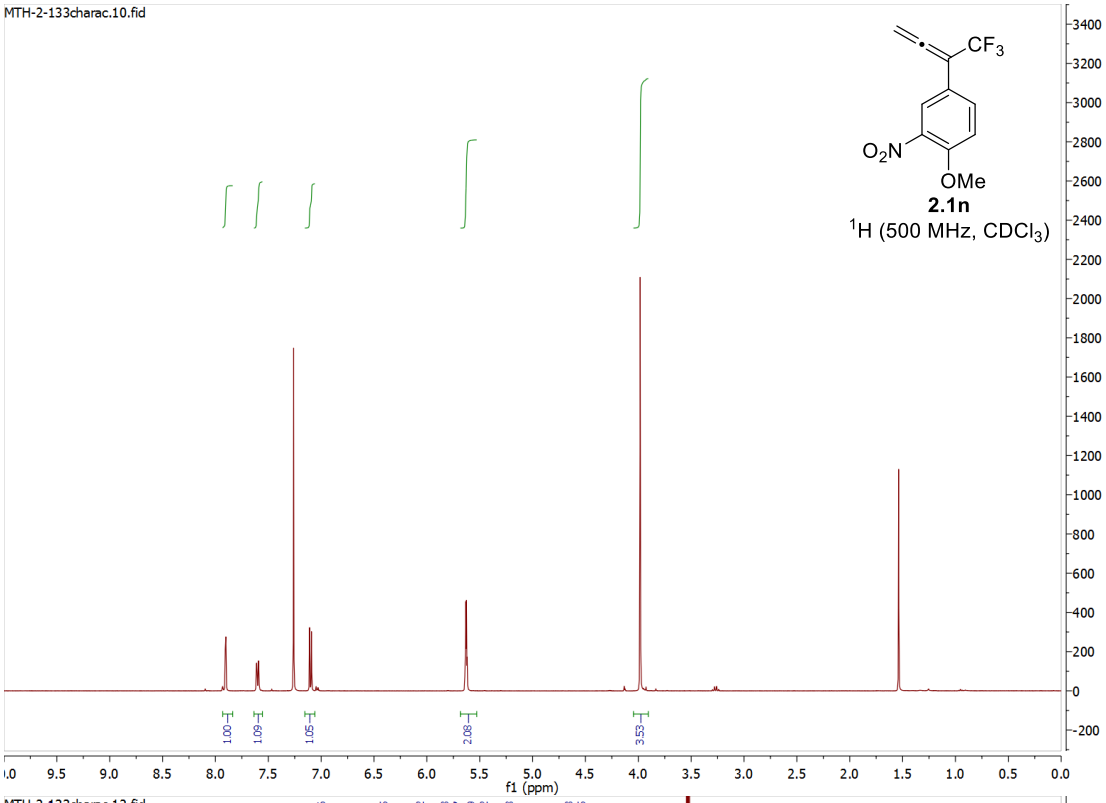
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.3 (q, *J* = 3.5 Hz), 153.8, 140.0, 132.4, 124.6, 123.1 (q, *J* = 272 Hz), 121.9, 114.0, 100.2 (q, *J* = 32 Hz), 84.9, 56.8.

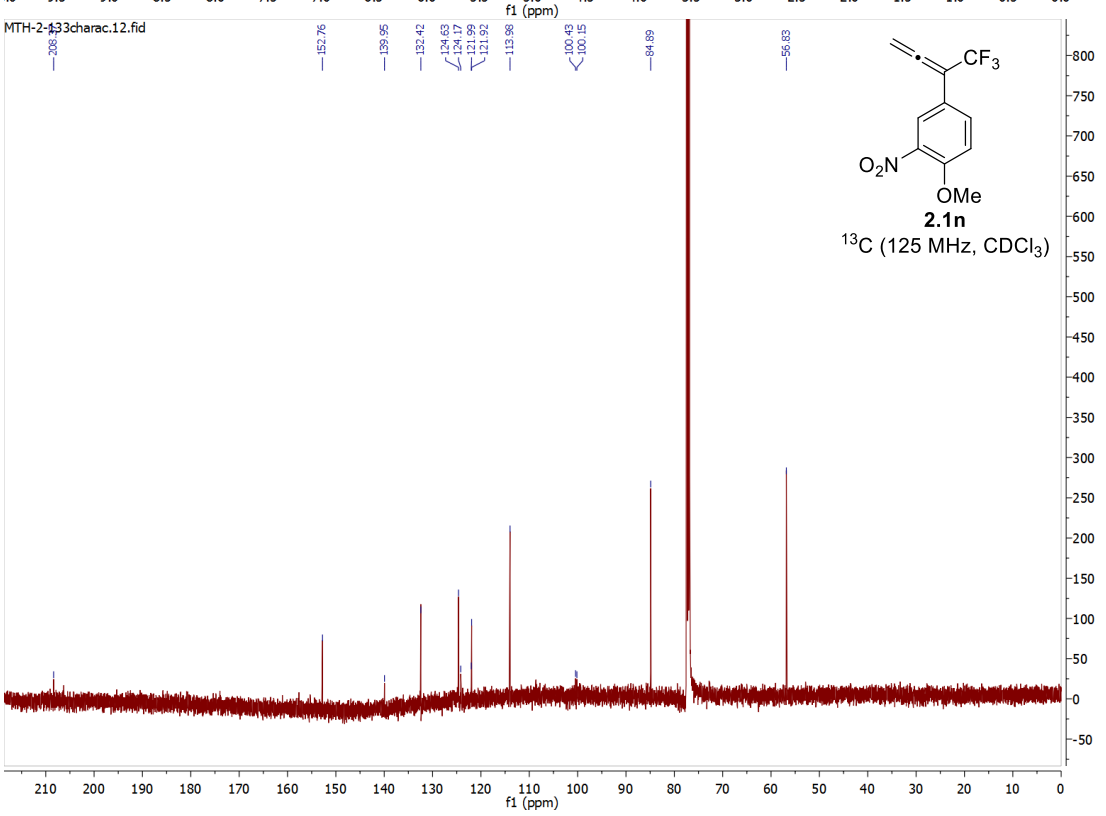
^{19}F NMR (470 MHz, $CDCl_3$) δ: -60.8 (t, *J* = 3.3 Hz).

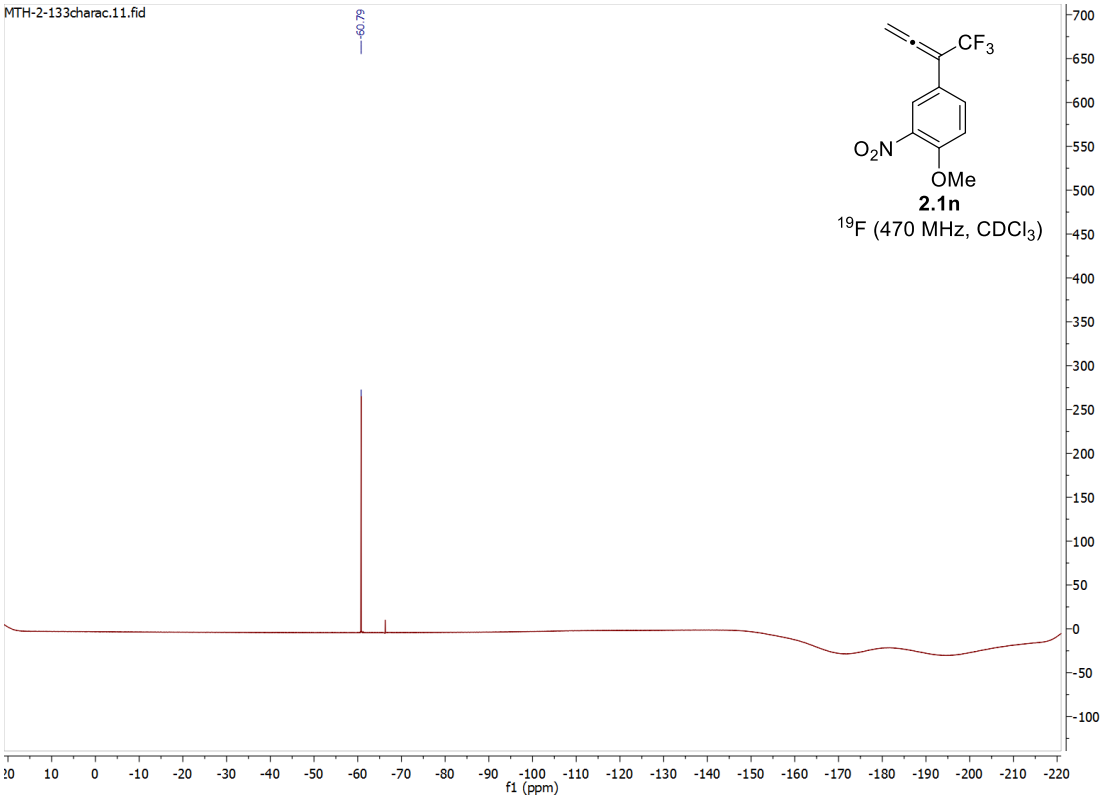
HRMS (CI+, *m/z*) for $C_{11}H_8F_3O_3N$ = 259.0456; found = 259.0461.

FTIR (neat): 2981, 2844, 1976, 1942, 1621, 1531, 1352, 1274, 1090, 1016, 870, 821 cm^{-1}

MP = 83-84 °C

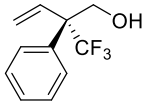

MTH-2-133charac.10.fid
CF3
O2N
OMe
2.1n
1H (500 MHz, CDCl3)
1.00
1.09
1.05
2.08
3.53
f1 (ppm)


MTH-2-133charac.12.fid
208.72
152.76
139.95
132.42
124.63
124.17
121.99
121.92
113.98
100.43
100.15
84.89
56.83
CF3
O2N
OMe
2.1n
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-133charac.11.fid
-60.79
CF3
O2N
OMe
2.1n
19F (470 MHz, CDCl3)
f1 (ppm)

2.5.3.3 Procedures and Spectral Data for Coupling Products of Methanol and Trifluoromethylallenes 2.1[a–o]

(*S*)-2-phenyl-2-(trifluoromethyl)but-3-en-1-ol (2.2a)



2.2a

Trifluoromethylallene **2.1a** (27.6 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2a** (24.5 mg, 0.11 mmol) was obtained as a light yellow oil in 76% yield. The addition of TBAI (10 mol%) afforded the title compound **2.2a** in 95% yield

R_f = 0.25 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: δ 7.52 – 7.47 (m, 2H), 7.43 – 7.33 (m, 3H), 6.13 (dd, *J* = 11.2, 17.8 Hz 1H), 5.62 (d, *J* = 11.2 Hz, 1H), 5.40 (d, *J* = 17.8 Hz, 1H), 4.26 (ddd, *J* = 11.9, 6.9, 0.5 Hz, 1H), 4.17 (ddd, *J* = 11.9, 7.0, 0.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.8 (s), 134.0 (q, *J* = 1.9 Hz), 129.1 (q, *J* = 1.3 Hz), 128.7, 128.4, 126.8 (q, *J* = 284.7 Hz), 120.76, 63.6 (q, *J* = 2.4 Hz), 57.1 (q, *J* = 22.9 Hz).

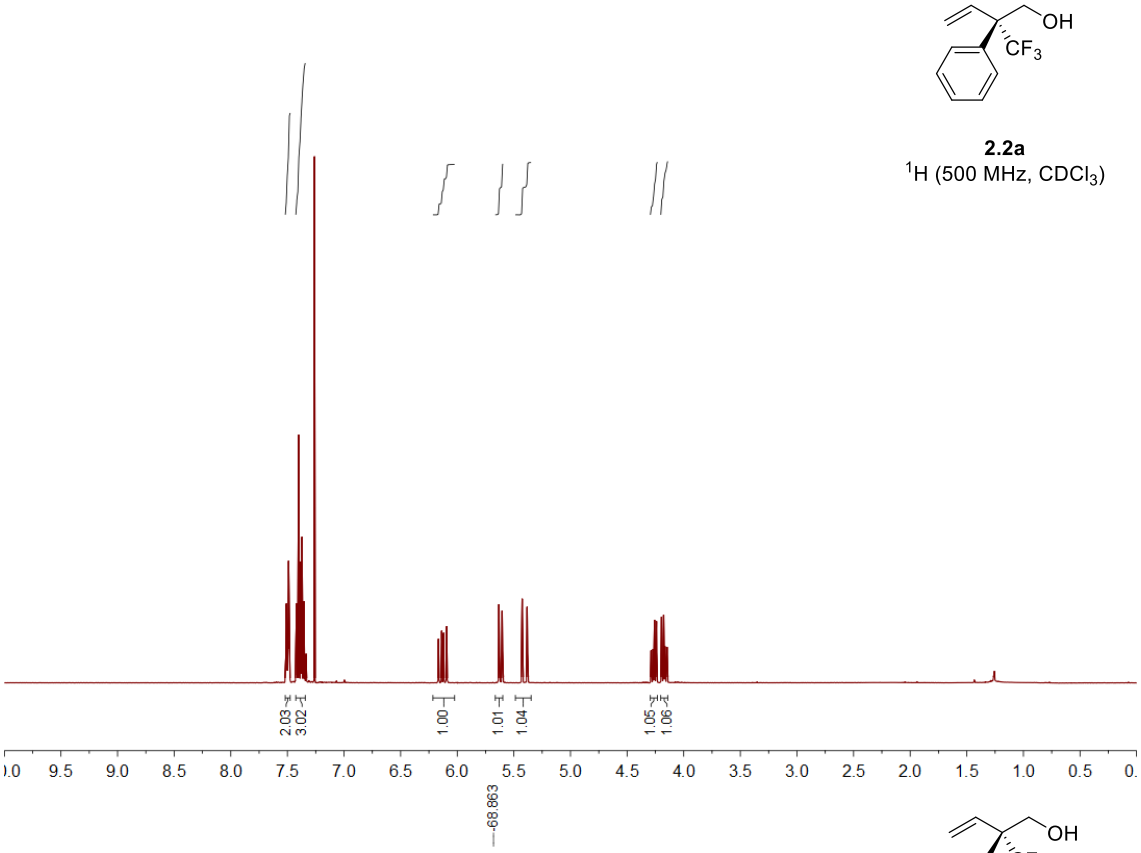
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.9.

HRMS (CI+, *m/z*) for $C_{11}H_{11}F_3O$: calcd. = $C_{11}H_{11}F_3O$ = 216.0762; found = 216.0761.

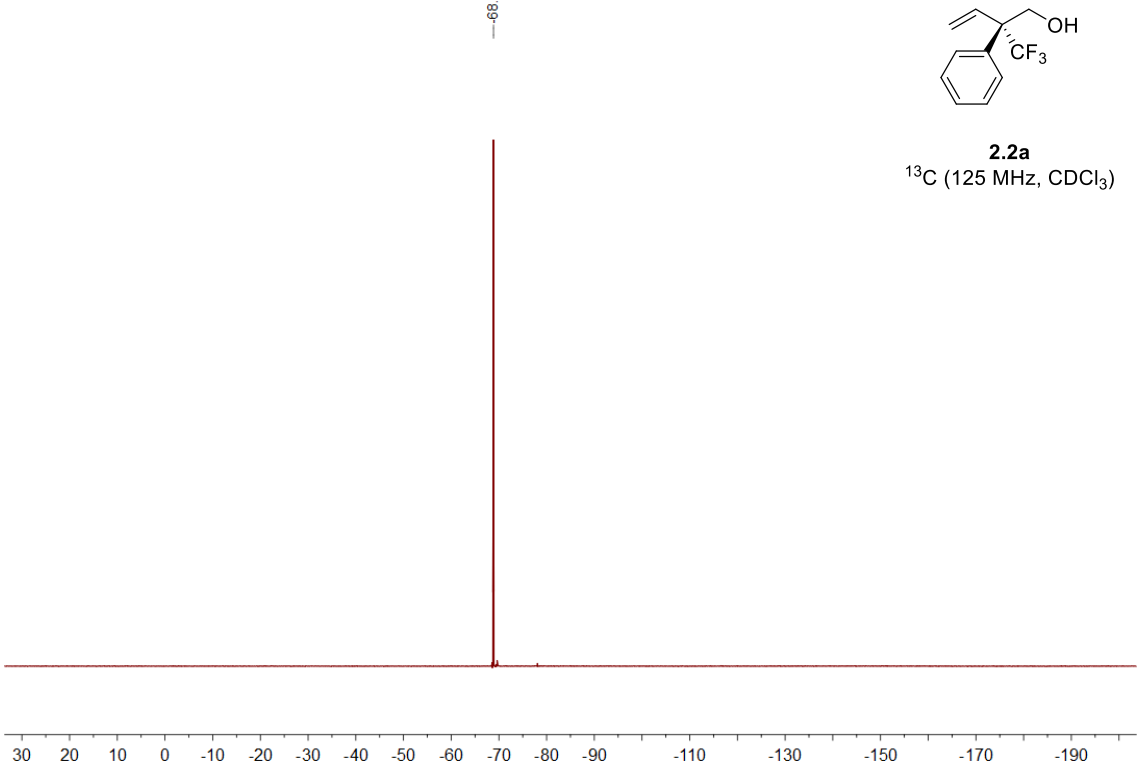
FTIR (neat): 3403, 2961, 2363, 1585, 1414, 1252, 1146, 1066, 935, 878, 699 cm^{-1}.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 89% or 90% (10 mol% TBAI).

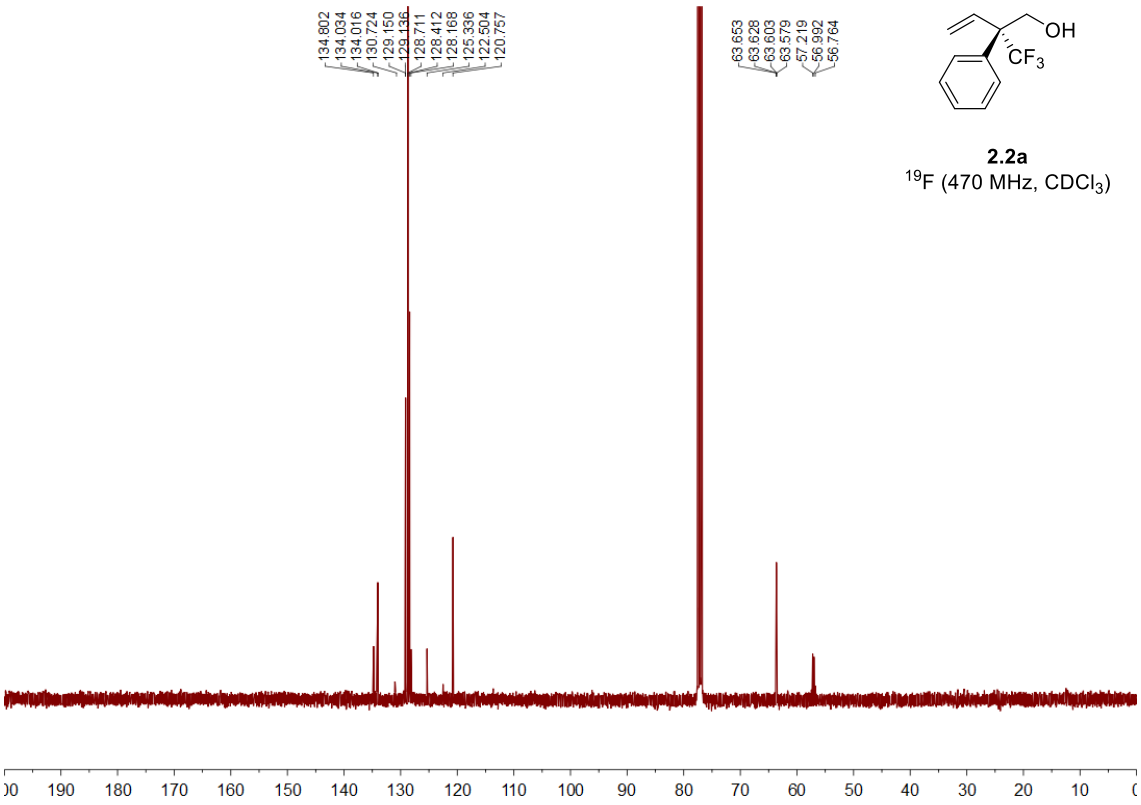
$[\alpha]_D^{24}$**=** +25.9 (c = 1.1, $CHCl_3$).

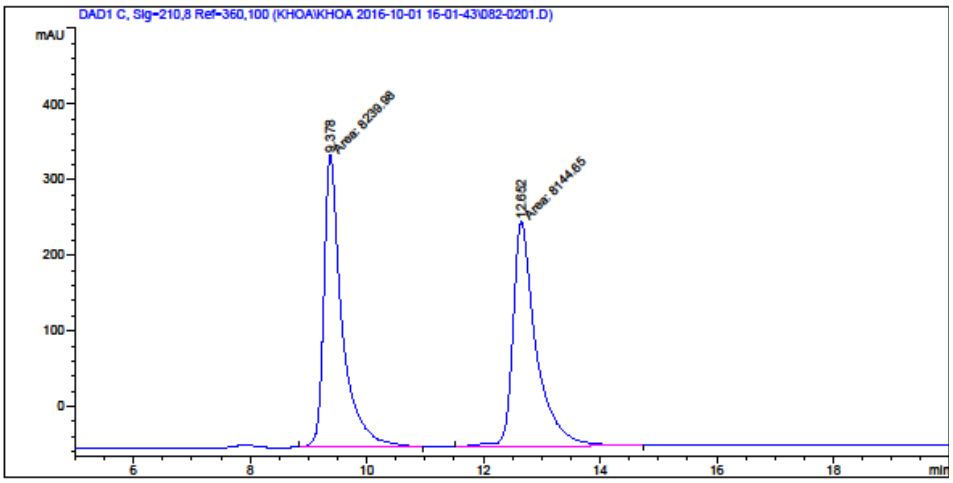


2.2a
^{1}H (500 MHz, $CDCl_3$)

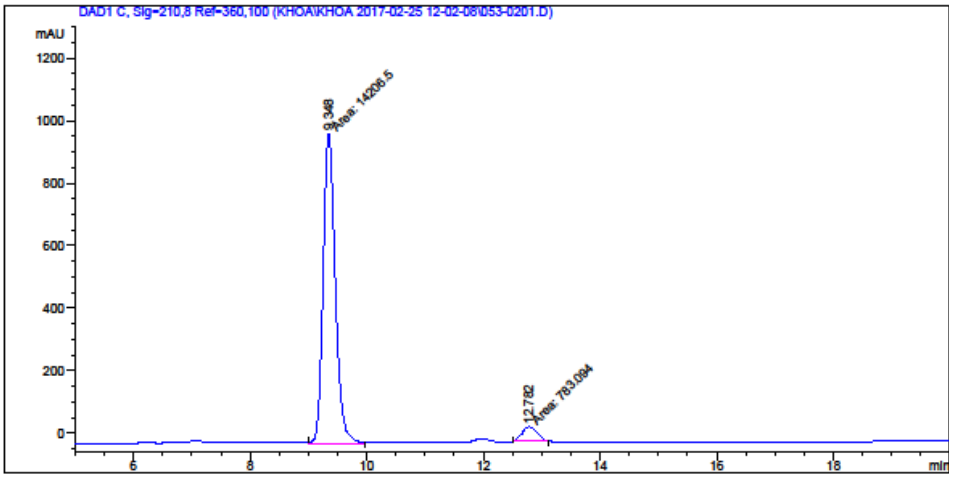


2.2a
^{13}C (125 MHz, $CDCl_3$)


134.802
134.034
134.016
130.724
129.150
129.136
128.711
128.412
128.168
125.336
122.504
120.757
63.653
63.628
63.603
63.579
57.219
56.992
56.764
OH
CF3
2.2a
19F (470 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

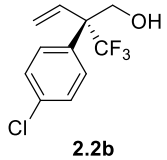


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.378	MM	0.3564	8239.97949	385.37039	50.2909
2	12.652	MM	0.4568	8144.65430	297.15997	49.7091



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.348	MM	0.2395	1.42065e4	988.76050	94.7758
2	12.782	MM	0.2835	783.09399	46.03831	5.2242

(*S*)-2-(4-chlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2b)



2.2b

Trifluoromethylallene **2.1b** (32.7 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2b** (29.0 mg, 0.12 mmol) was obtained as a light yellow oil in 77% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2b** in 62% yield.

R_f = 0.29 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.10 (dd, *J* = 12.3, 17.3 Hz, 1H), 5.62 (d, *J* = 12.3 Hz, 1H), 5.36 (d, *J* = 17.3 Hz, 1H), 4.24 (dd, *J* = 7.5, 11.8 Hz, 1H), 4.12 (dd, *J* = 7.5, 11.8 Hz, 1H), 1.58 (t, *J* = 7.5 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.6, 133.7, 133.3, 130.8, 128.8, 126.5 (q, *J* = 283 Hz), 121.2, 63.4 (q, *J* = 2.6 Hz), 56.8 (q, *J* = 24.0 Hz).

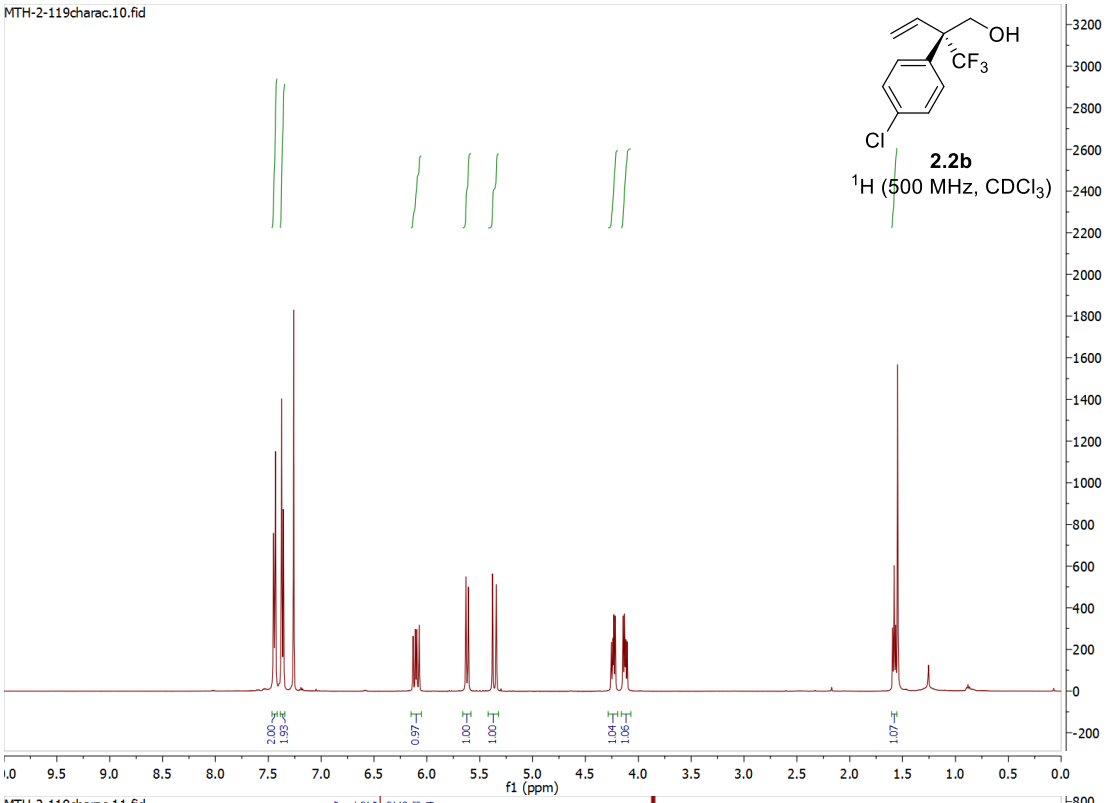
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.1.

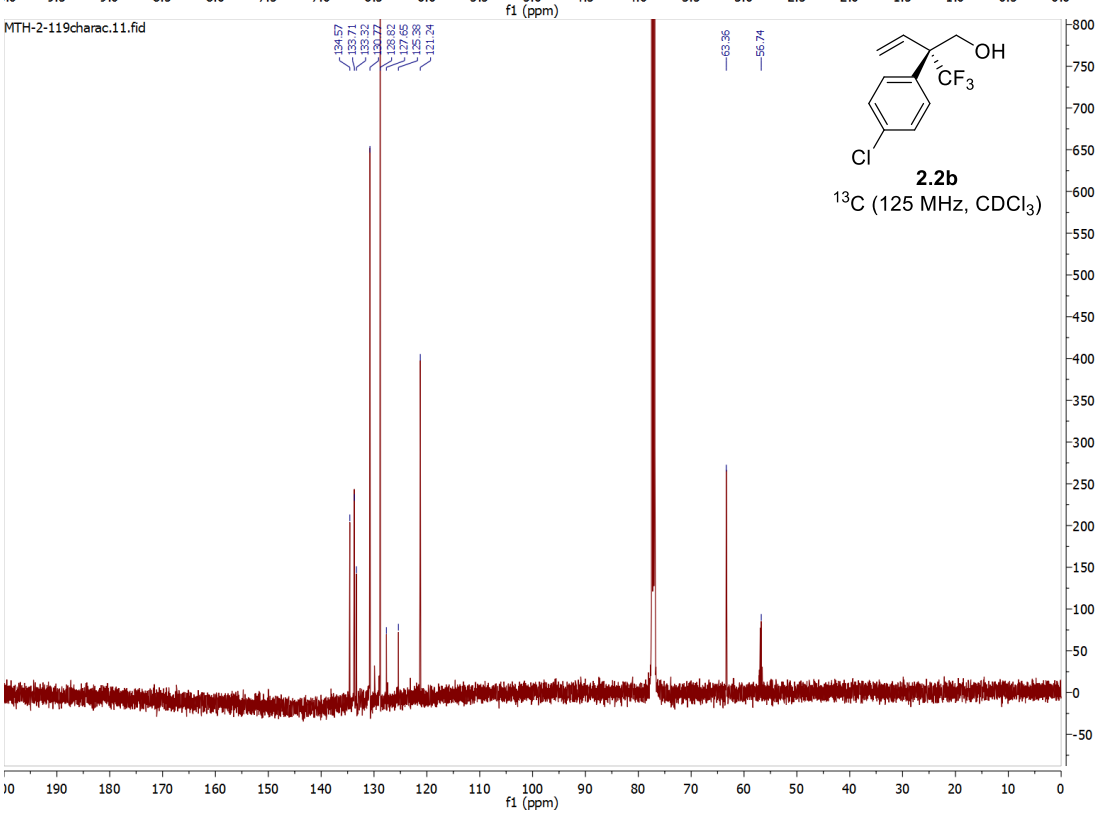
HRMS (CI+, *m/z*) for $C_{11}H_{10}OF_3Cl$ = 250.0372; found = 250.0374.

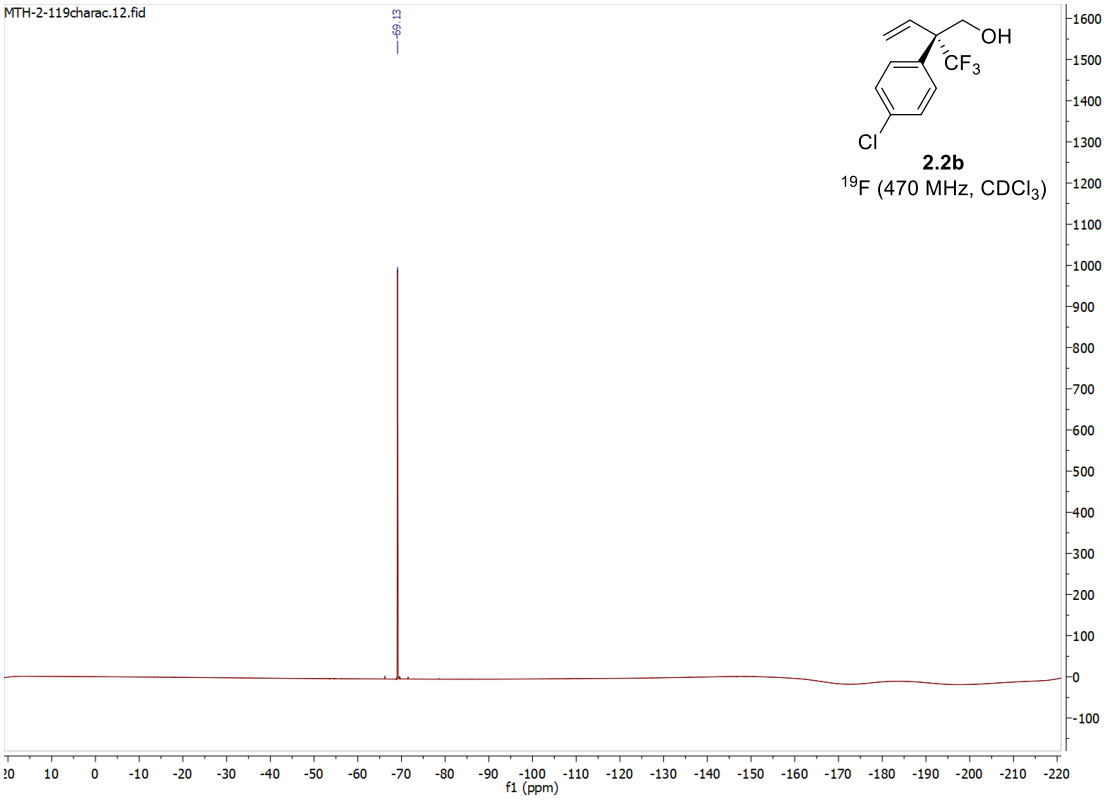
FTIR (neat): 3419, 2970, 2359, 1496, 1366, 1151, 1098, 1014, 936, 822, 747 cm^{-1}.

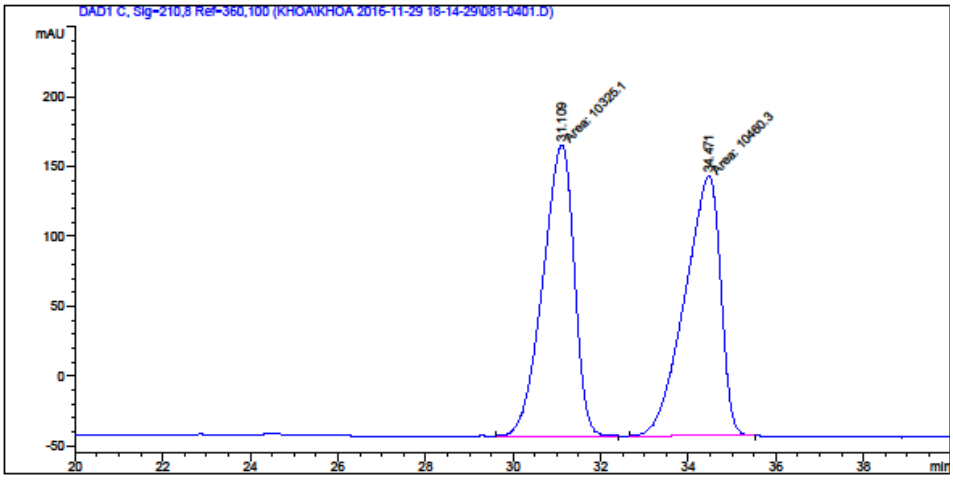
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 86% or 90% (500 mol% H_2O).

$[\alpha]_D^{27}$ = +17.5 (c = 1.0, $CHCl_3$).

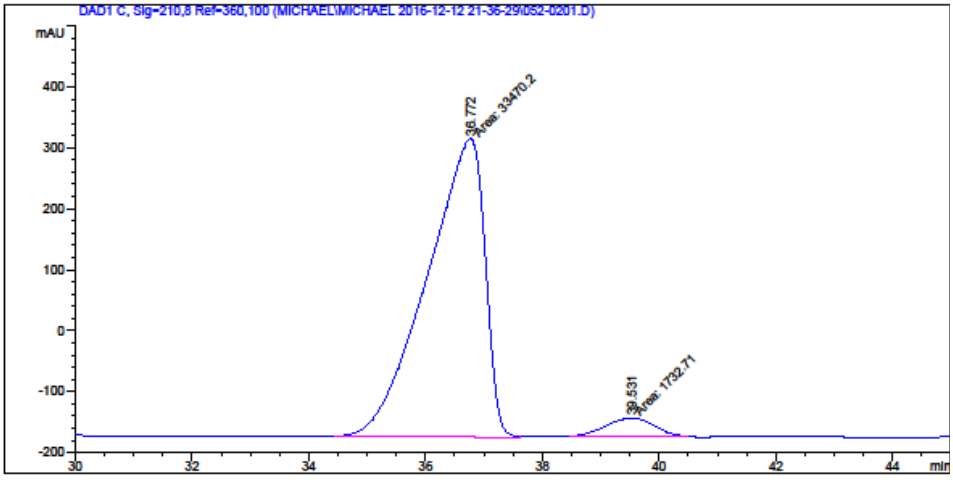

MTH-2-119charac.10.fid
OH
CF3
Cl
2.2b
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-119charac.11.fid
134.57
133.71
133.21
130.77
128.82
127.65
125.38
121.24
63.36
56.74
OH
CF3
Cl
2.2b
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-119charac.12.fid
-69.13
OH
CF3
Cl
2.2b
19F (470 MHz, CDCl3)
f1 (ppm)

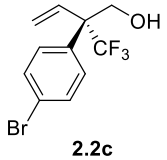


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.109	MM	0.8255	1.03251e4	208.46031	49.6747
2	34.471	MM	0.9398	1.04603e4	185.50821	50.3253



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.772	MM	1.1408	3.34702e4	488.98523	95.0779
2	39.531	MM	0.9489	1732.70776	30.43362	4.9221

(*S*)-2-(4-bromophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2c)



2.2c

Trifluoromethylallene **2.1c** (39.5 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2c** (34.8 mg, 0.12 mmol) was obtained as a light yellow oil in 79% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2c** in 60% yield.

R_f = 0.27 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.10 (dd, *J* = 11.4, 18.0 Hz, 1H), 5.62 (d, *J* = 11.4 Hz, 1H), 5.36 (d, *J*= 18.0 Hz, 1H), 4.23 (dd, *J* = 7.1, 11.9 Hz, 1H), 4.12 (dd, *J* = 7.1, 11.9 Hz, 1H), 1.57 (t, *J* = 7.1 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 133.9, 133.6, 131.8, 131.0, 126.4 (q, *J* = 286 Hz), 122.8, 121.3, 63.3, 56.9 (q, *J* = 22 Hz).

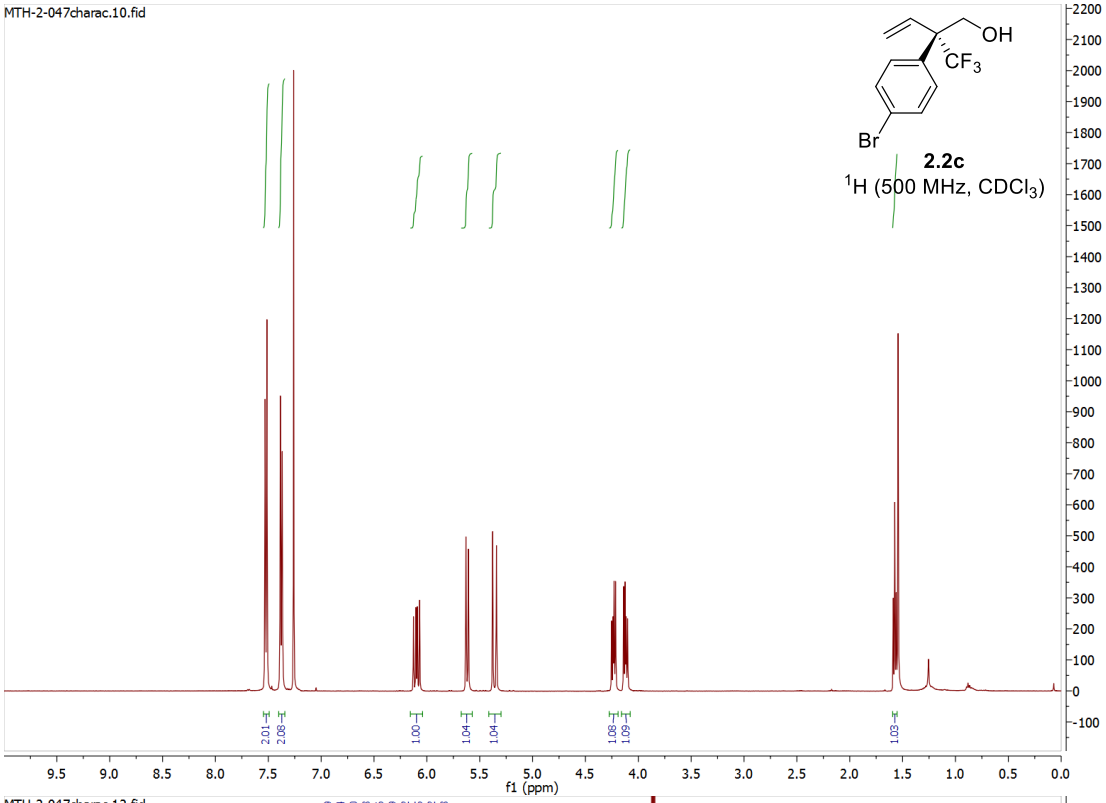
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.1.

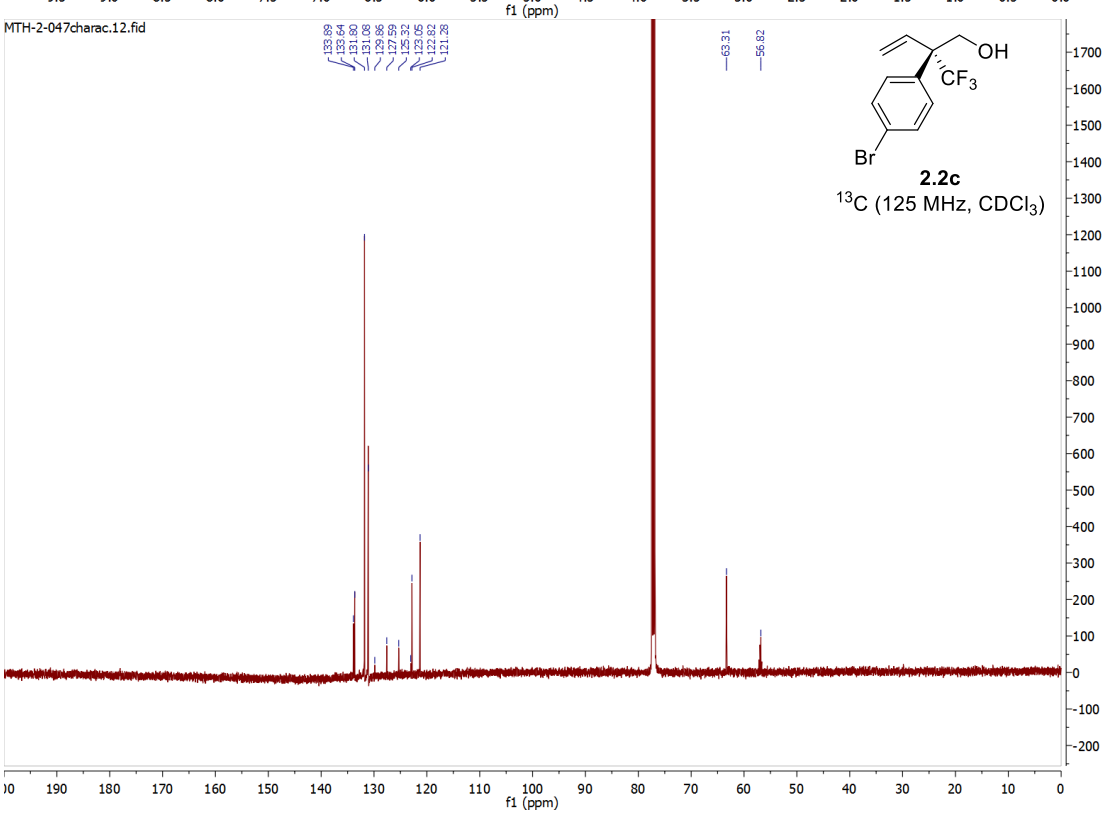
HRMS (CI+, *m/z*) for $C_{11}H_{10}OF_3Br$ = 293.9867; found = 293.9869.

FTIR (neat): 3409, 2964, 2360, 1493, 1259, 1153, 1079, 1010, 818 cm^{-1}.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 87% or 91% (500 mol% H_2O).

$[\alpha]_D^{27}$ = +16.7 (c = 1.0, $CHCl_3$).


MTH-2-047charac.10.fid
OH
CF3
Br
2.2c
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-047charac.12.fid
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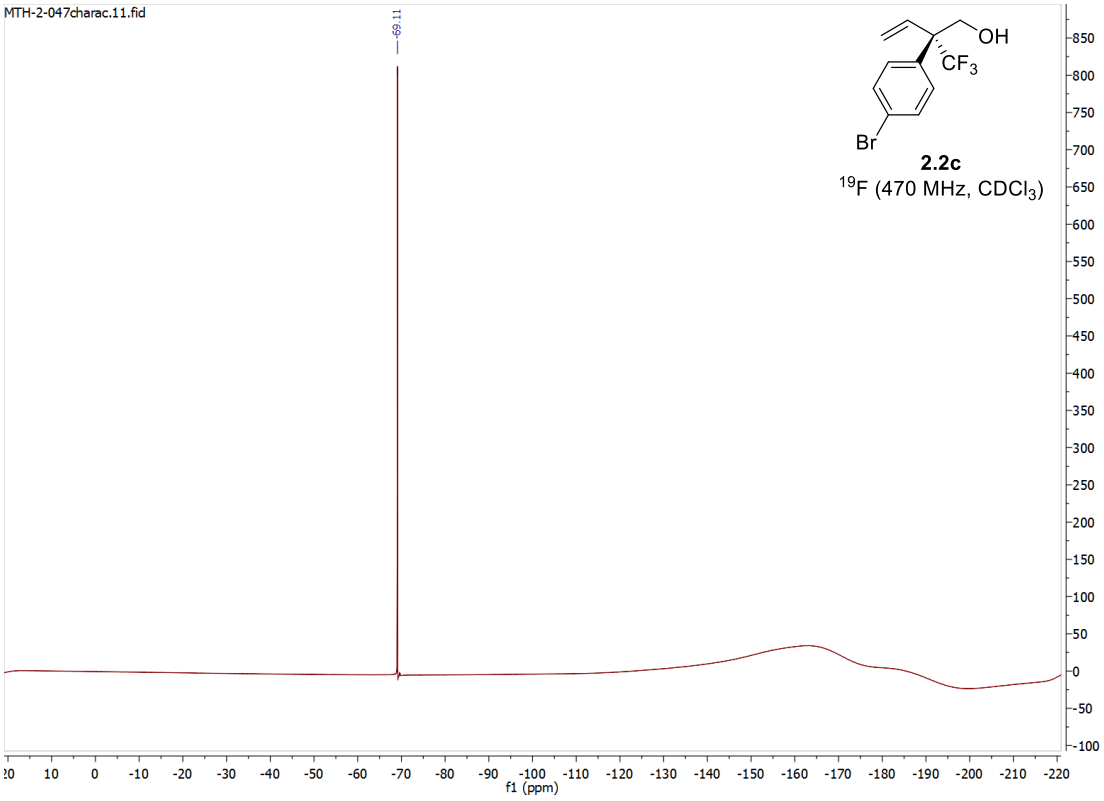
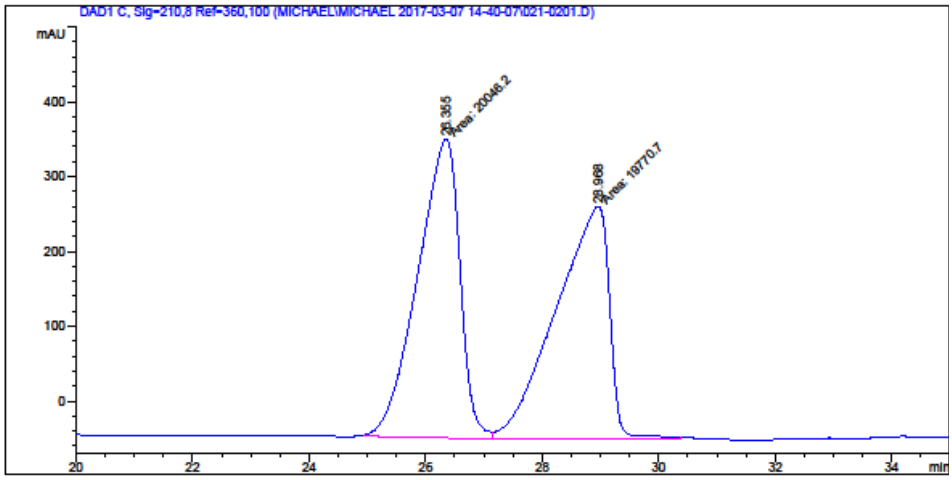
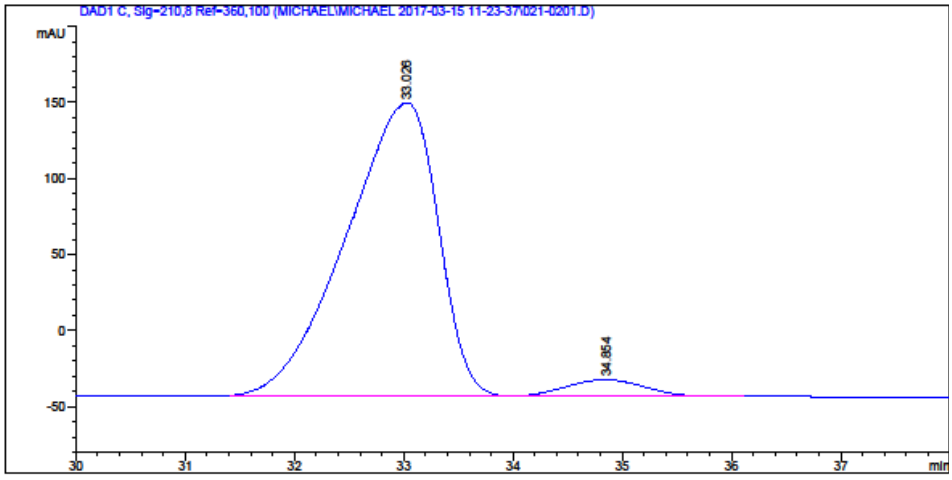
133.64
131.80
131.08
129.56
127.59
125.32
123.05
122.82
121.28
63.31
56.82
OH
CF3
Br
2.2c
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-047charac.11.fid
-69.11
OH
CF3
Br
2.2c
19F (470 MHz, CDCl3)
f1 (ppm)

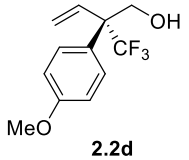


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.355	MM	0.8382	2.00462e4	398.62067	50.3460
2	28.968	MM	1.0610	1.97707e4	310.56766	49.6540



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.026	BV	0.8432	1.12237e4	192.78250	95.4818
2	34.854	VB	0.6034	531.10510	10.88113	4.5182

(*S*)-2-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2d)



2.2d

Trifluoromethylallene **2.1d** (32.1 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2d** (33.3 mg, 0.14 mmol) was obtained as a light yellow oil in 90% yield. The addition of TBAI (10 mol%) afforded the title compound **2.2d** in 93% yield.

R_f = 0.37 (hexanes:EtOAc = 3:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.11 (dd, *J* = 10.4, 17.4 Hz, 1H), 5.60 (d, *J* = 10.4 Hz, 1H), 5.39 (d, *J* = 17.4 Hz, 1H), 4.22 (dd, *J* = 5.5, 10.8 Hz, 1H), 4.13 (dd, *J* = 5.5, 10.8 Hz, 1H), 3.82 (s, 3H), 1.55 (t, *J* = 5.5 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.5, 134.2, 130.4, 126.8 (q, *J* = 282 Hz), 126.5, 120.6, 114.1, 63.5, 56.5 (q, *J* = 24 Hz), 55.4.

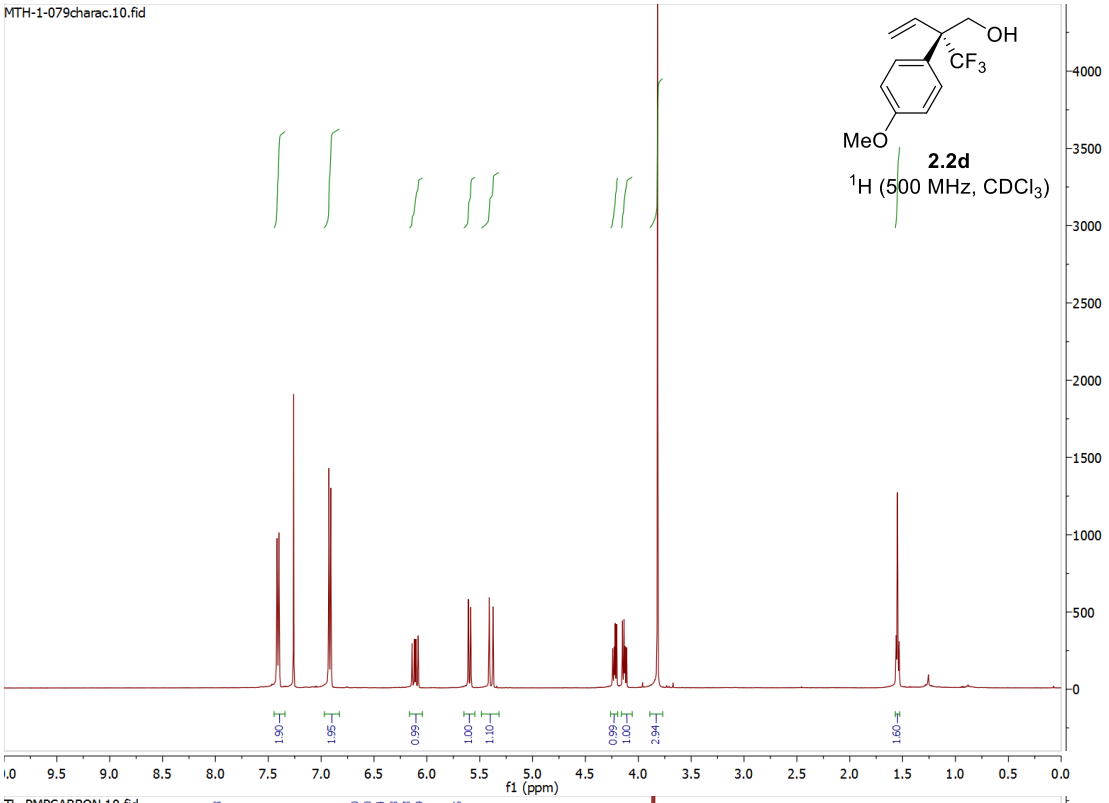
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.3.

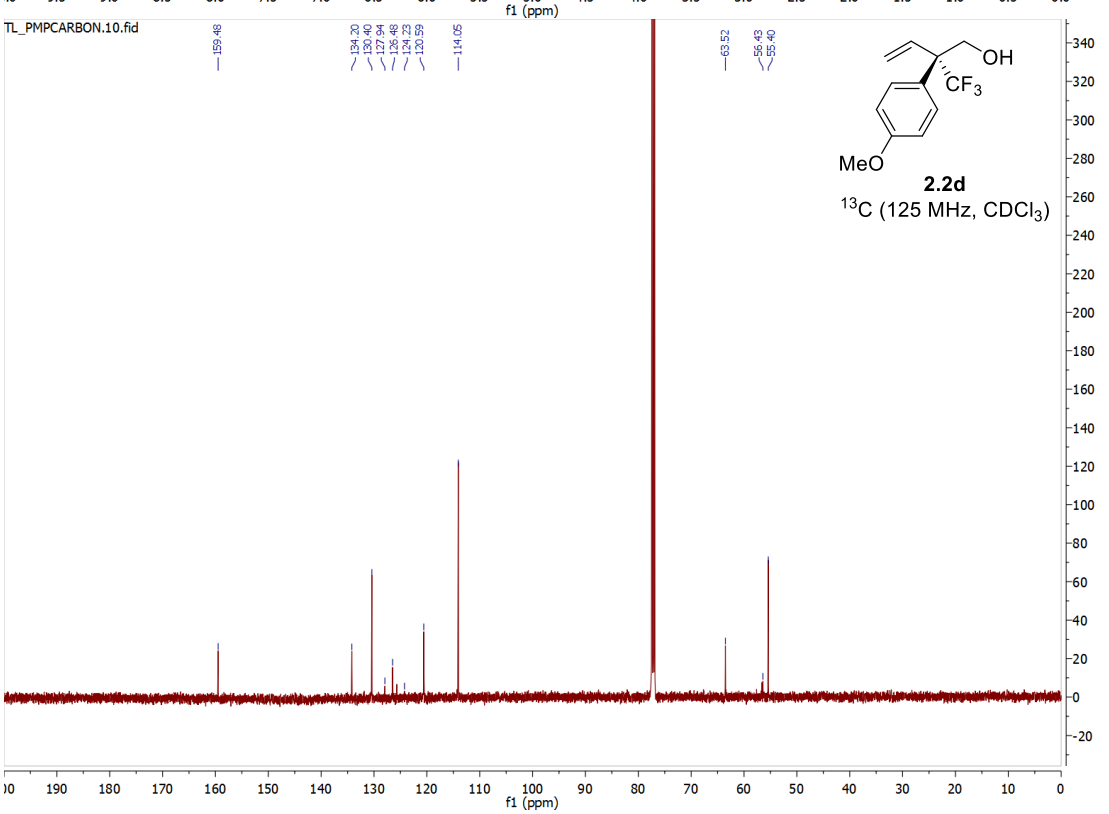
HRMS (CI+, *m/z*) for $C_{12}H_{13}O_2F_3$: calcd. = 246.0868; found = 246.0871.

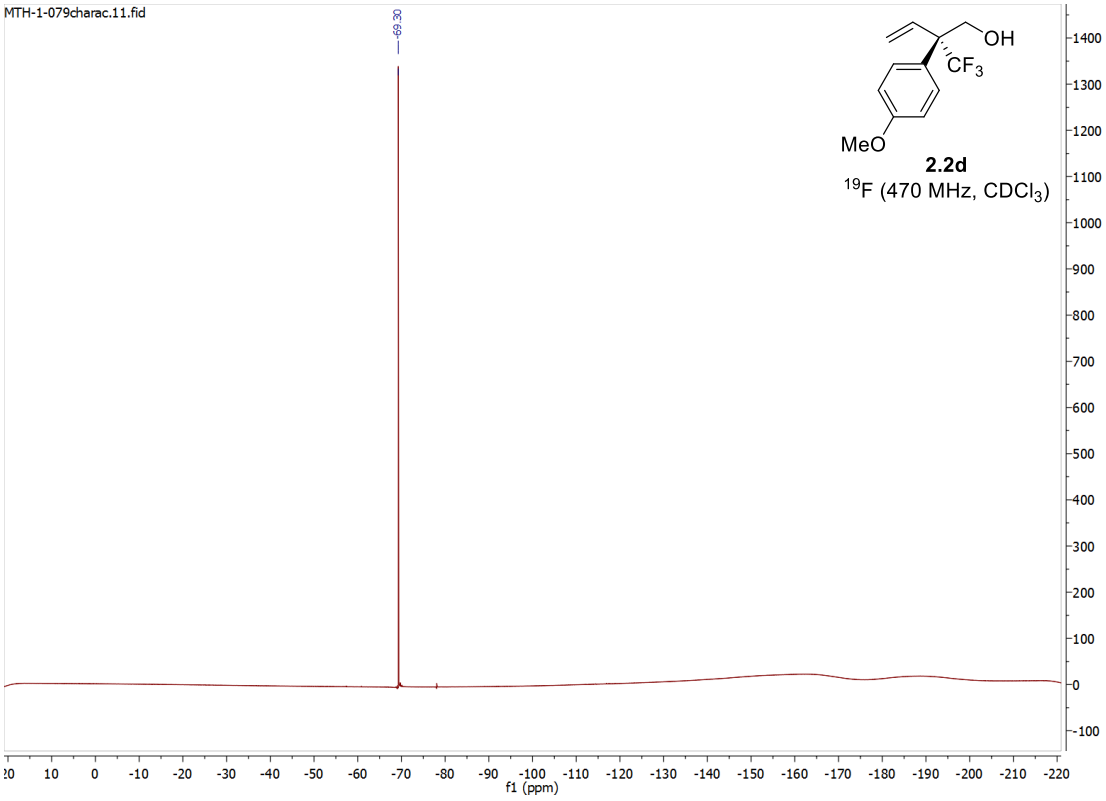
FTIR (neat):3485, 2937, 2840, 1612, 1515, 1465, 1524, 1147, 1036, 933, 828, 738 cm^{-1}.

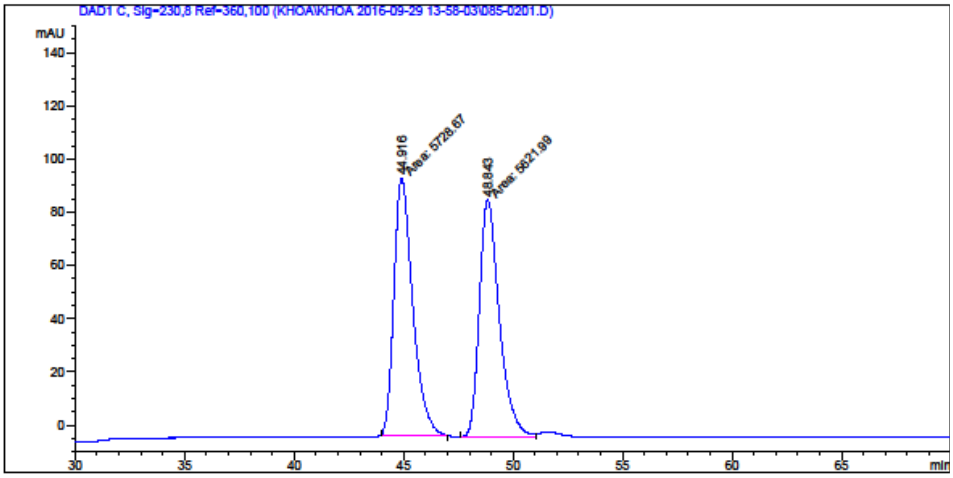
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 89% or 90% (10 mol% TBAI).

$[\alpha]_D^{27}$ = +20.0 (c = 1.0, $CHCl_3$).

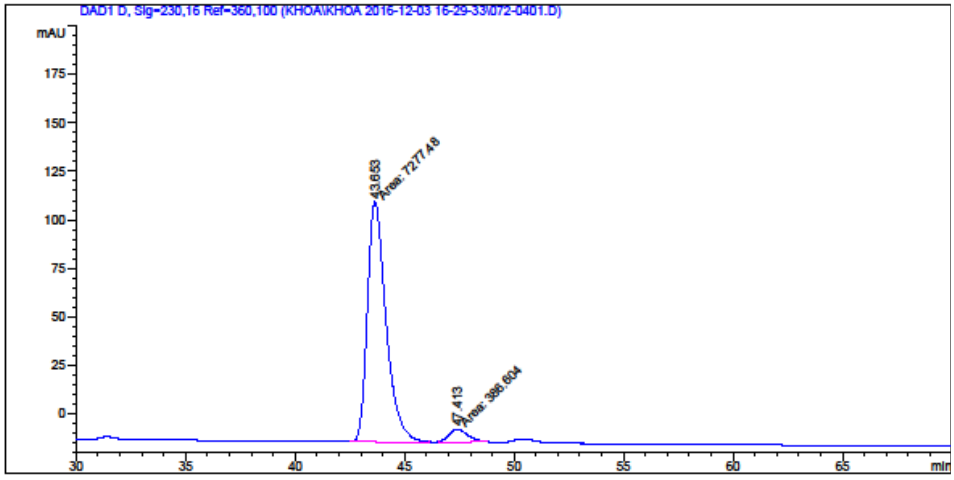

MTH-1-079charac.10.fid
OH
CF3
MeO
2.2d
1H (500 MHz, CDCl3)
f1 (ppm)


TL_PMPCARBON.10.fid
159.48
134.20
130.40
127.94
124.48
124.23
120.59
114.05
63.52
56.43
55.40
OH
CF3
MeO
2.2d
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-1-079charac.11.fid
-69.30
OH
CF3
MeO
2.2d
19F (470 MHz, CDCl3)
f1 (ppm)

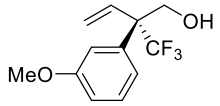


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.916	MM	0.9890	5728.66895	96.53577	50.4699
2	48.843	MM	1.0514	5621.99170	89.11501	49.5301



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.653	MM	0.9804	7277.47803	123.71993	94.9556
2	47.413	MM	0.9896	386.60403	6.51129	5.0444

(*S*)-2-(3-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2e)



2.2e

Trifluoromethylallene **2.1e** (32.1 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2e** (31.0mg, 0.13 mmol) was obtained as a light yellow oil in 84% yield.

R_f = 0.39 (3:1 hexanes/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.05 (br s, 1H), 6.90 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.10 (dd, *J* = 11.8, 18.0 Hz, 1H), 5.61 (d, *J* = 11.8 Hz, 1H), 5.43 (d, *J* = 18.0 Hz, 1H), 4.24 (dd, *J* = 6.9, 12.6 Hz, 1H), 4.15 (dd, *J* = 7.5, 12.6 Hz, 1H), 3.82 (s, 3H), 1.56 (t, *J* = 7.3 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.8, 136.3, 133.8, 129.7, 126.6 (q, *J* = 285 Hz), 121.2, 120.7, 115.9, 113.2, 63.7, 57.0 (q, *J* = 20.3 Hz), 55.4.

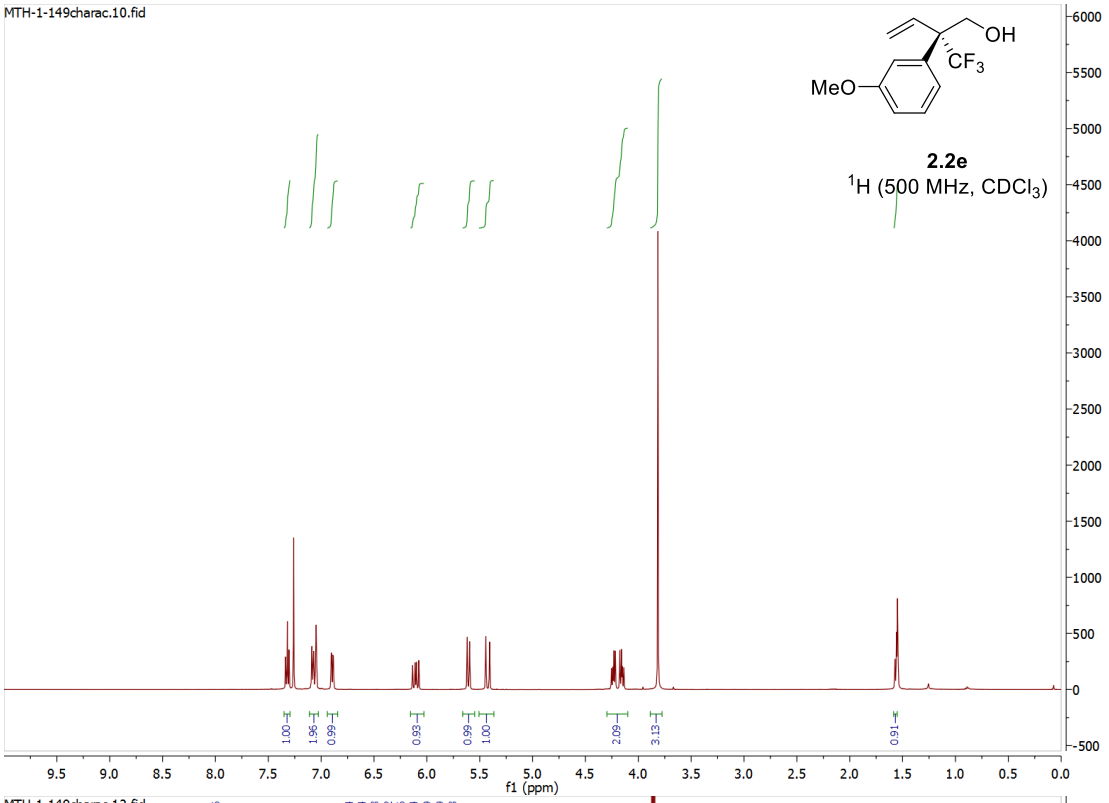
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.6.

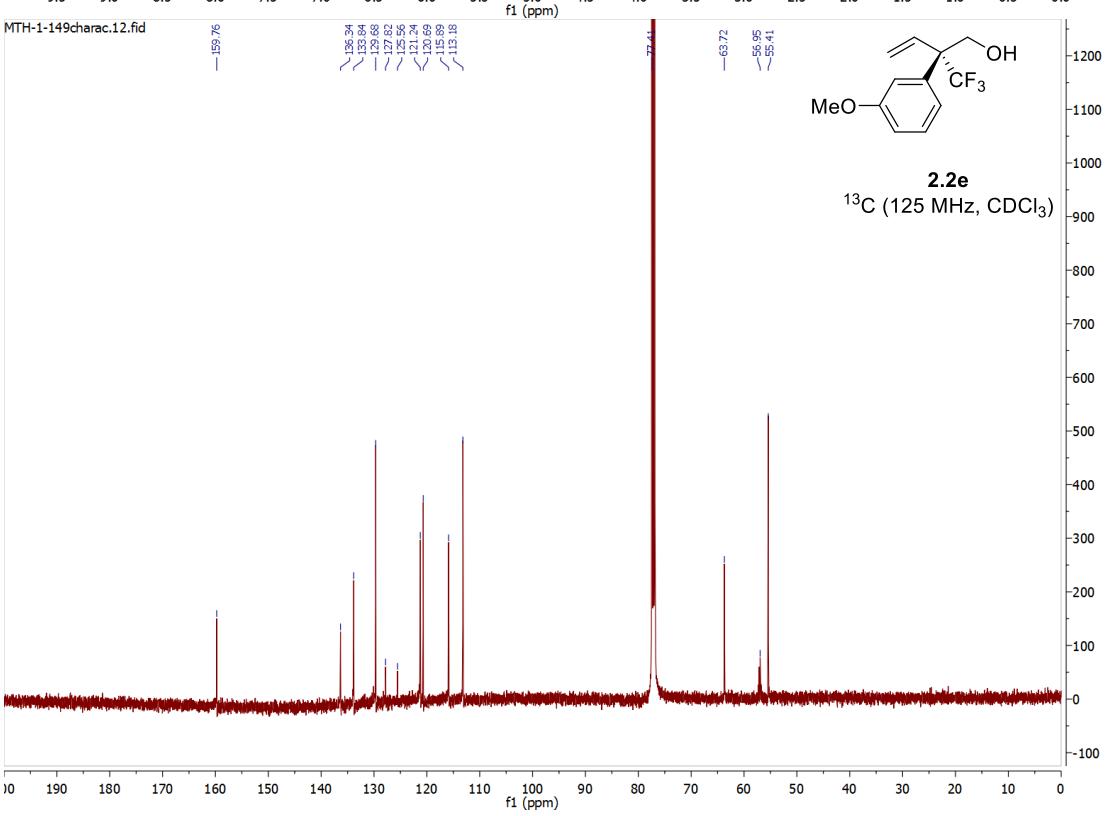
HRMS (CI+, *m/z*) for $C_{12}H_{13}O_2F_3$ = 246.0868; found = 246.0871.

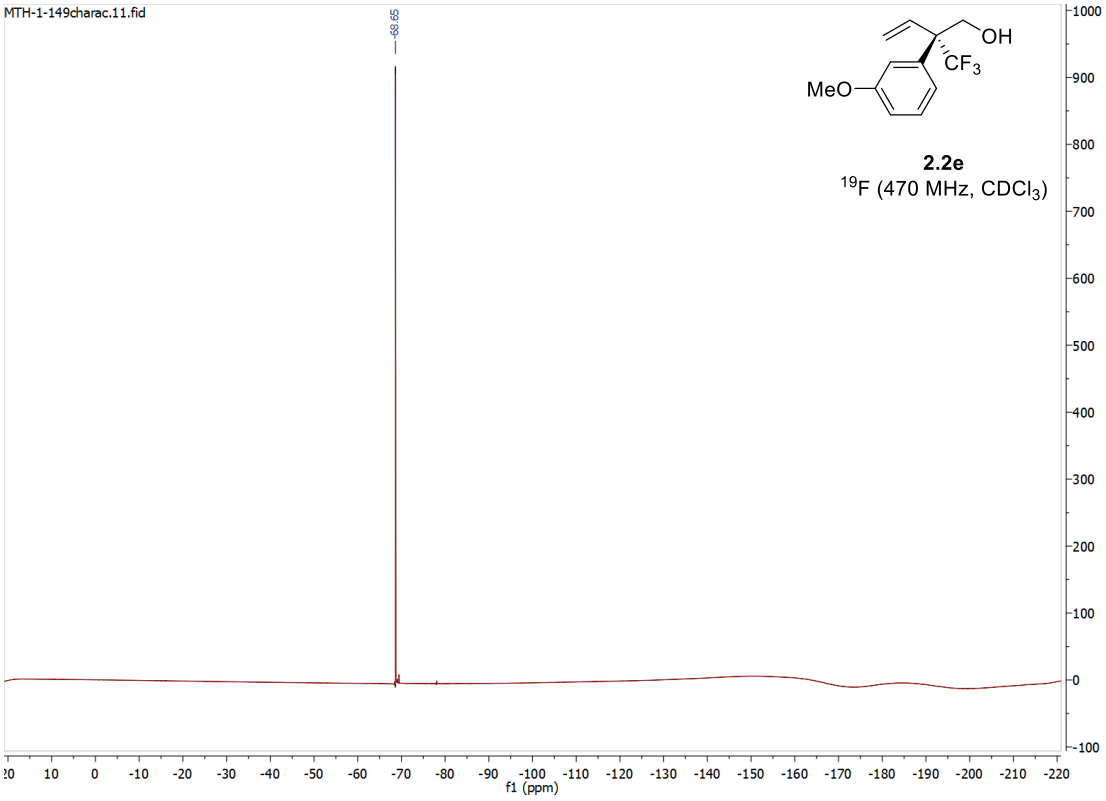
FTIR (neat): 3456, 2923, 2357, 1603, 1584, 1366, 1171, 1144, 1044, 940, 781, 701 cm^{-1}.

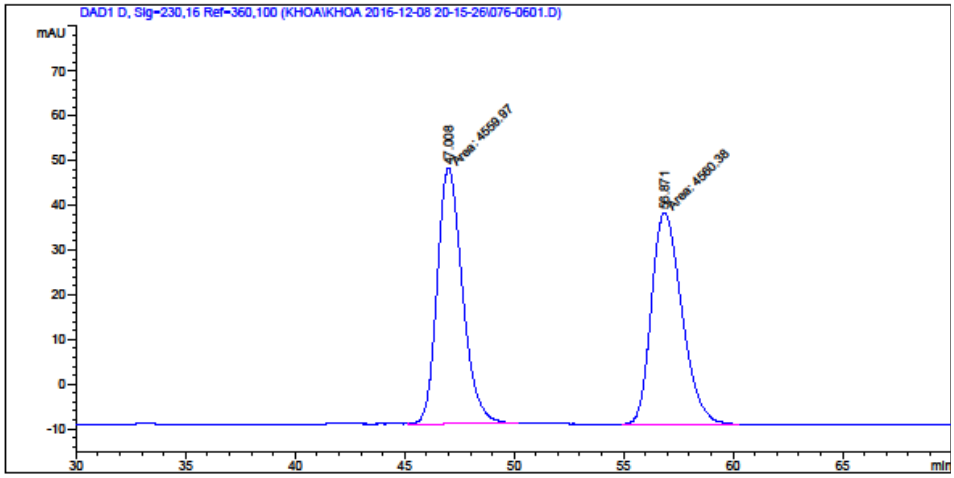
HPLC: (Chiralcel column AS-H, Hexane:2-PrOH = 99:1, 0.5 mL/min, 210 nm) ee = 90%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +17.1(c = 1.0, $CHCl_3$).

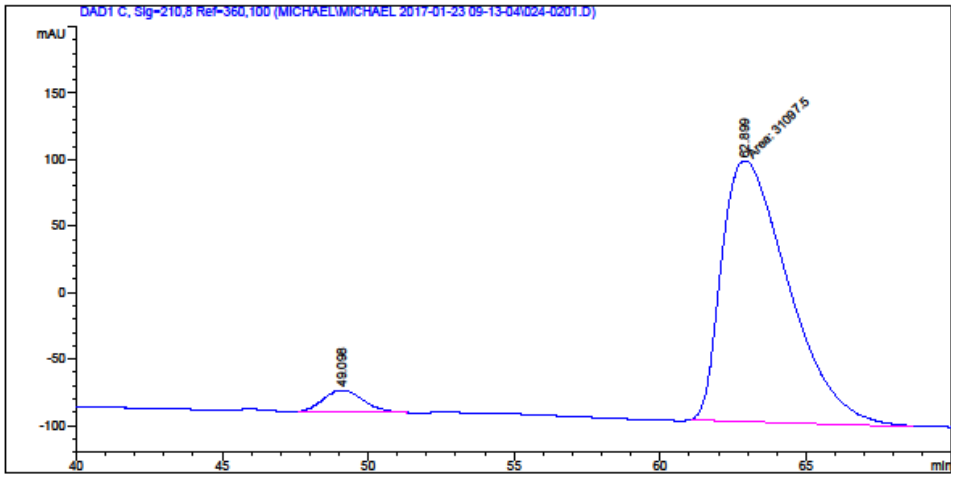

MTH-1-149charac.10.fid
OH
CF3
MeO
2.2e
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-1-149charac.12.fid
159.76
136.34
133.84
129.68
127.82
125.56
121.24
120.69
115.89
113.18
77.41
63.72
56.95
55.41
OH
CF3
MeO
2.2e
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-1-149charac.11.fid
-68.65
OH
CF3
MeO
2.2e
19F (470 MHz, CDCl3)
f1 (ppm)

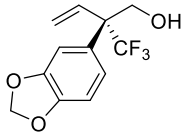


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.008	MM	1.3298	4559.96973	57.15035	49.9978
2	56.871	MM	1.6059	4560.37988	47.32843	50.0022



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.098	BB	1.0998	1522.62524	16.36059	4.6678
2	62.899	MM	2.6440	3.10975e4	196.02737	95.3322

(*S*)-2-(benzo[d][1,3]dioxol-5-yl)-2-(trifluoromethyl)but-3-en-1-ol (2.2f)



2.2f

Trifluoromethylallene **2.1f** (34.2 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ and TBAI (10 mol%) in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2f** (30.8 mg, 0.12 mmol) was obtained as a light yellow oil in 79% yield.

R_f = 0.22 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.98 (m, 1H), 6.97 (m, 1H), 6.82 (dd, *J* = 0.5, 8.1 Hz, 1H), 6.08 (dd, *J* = 11.5, 18.1 Hz, 1H), 5.98 (s, 2H), 5.60 (d, *J* = 11.5 Hz, 1H), 5.41 (d, *J* = 18.1 Hz, 1H), 4.19 (dd, *J* = 6.7, 12.2 Hz, 1H), 4.10 (dd, *J* = 7.4, 12.2 Hz, 1H), 1.56 (dd, *J* = 6.7, 7.4 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.1, 147.6, 134.0, 128.2, 126.7 (q, *J* = 288 Hz), 123.3, 122.9, 109.8, 108.3, 101.5, 63.6, 56.7 (q, *J* = 25.5 Hz).

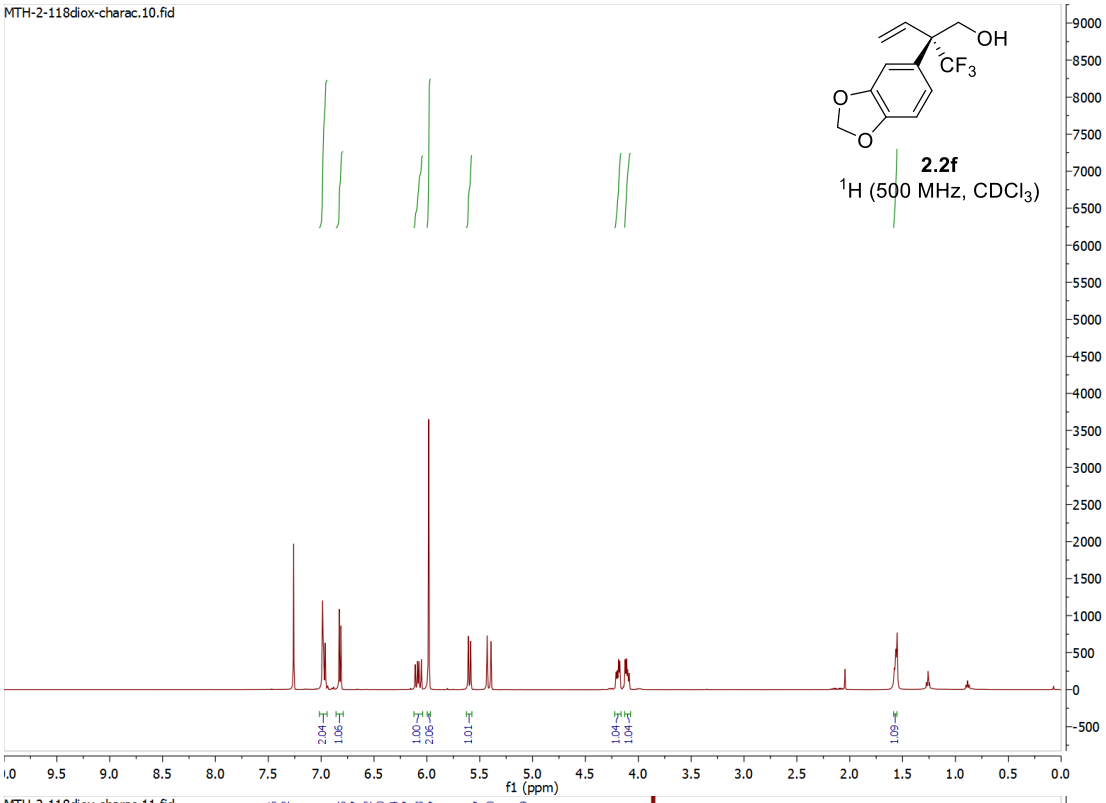
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.2.

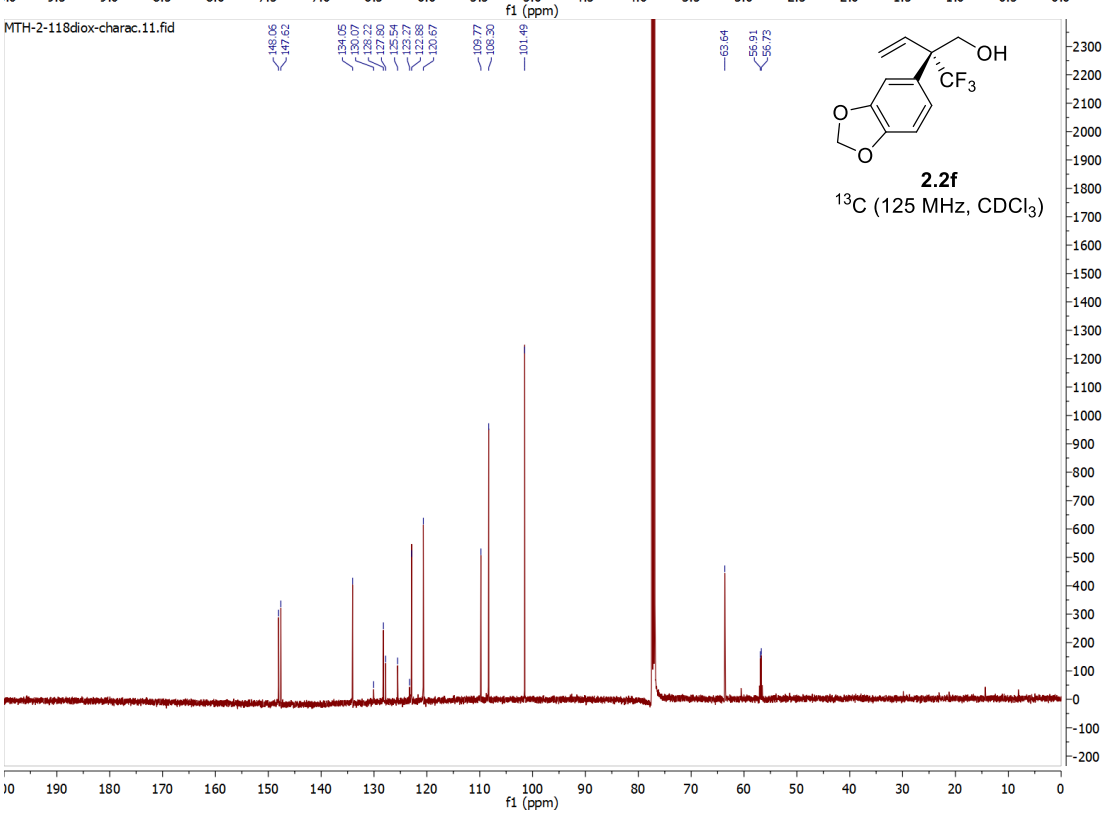
HRMS (CI+, *m/z*) for $C_{12}H_{11}O_3F_3$ = 260.0660; found = 260.0661.

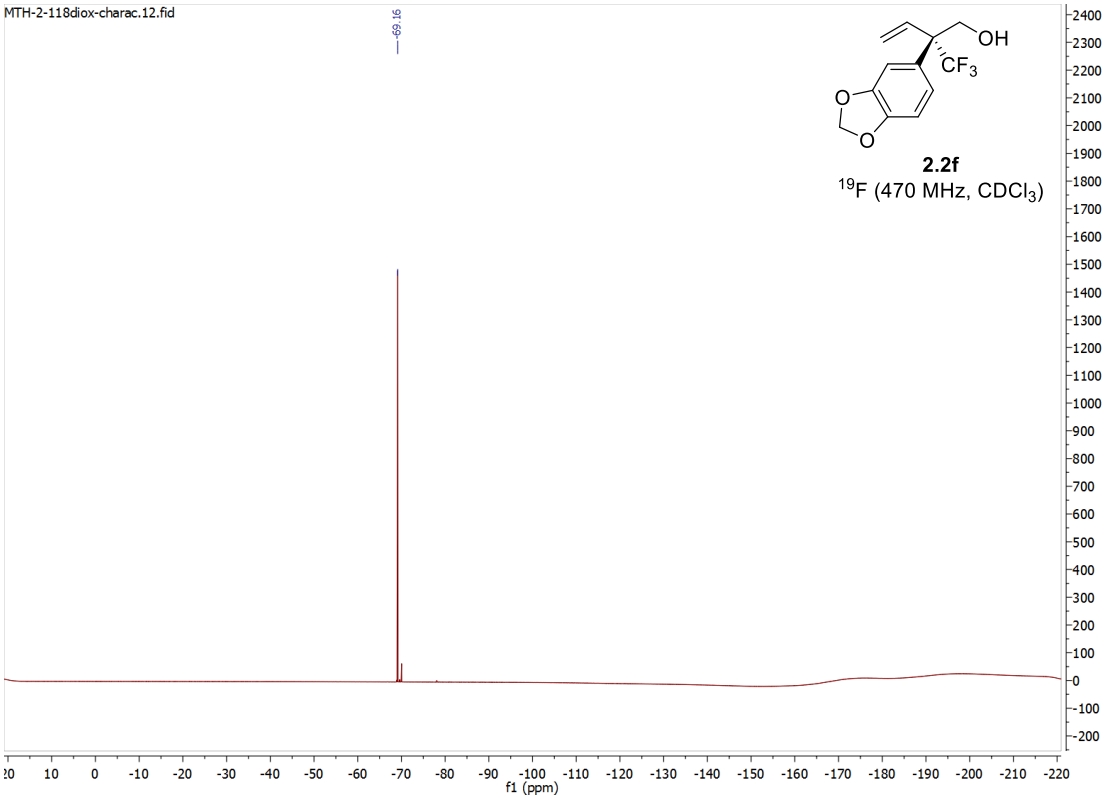
FTIR (neat): 3444, 2901, 2358, 1736, 1507, 1491, 1241, 1161, 1040, 935, 814 cm^{-1}.

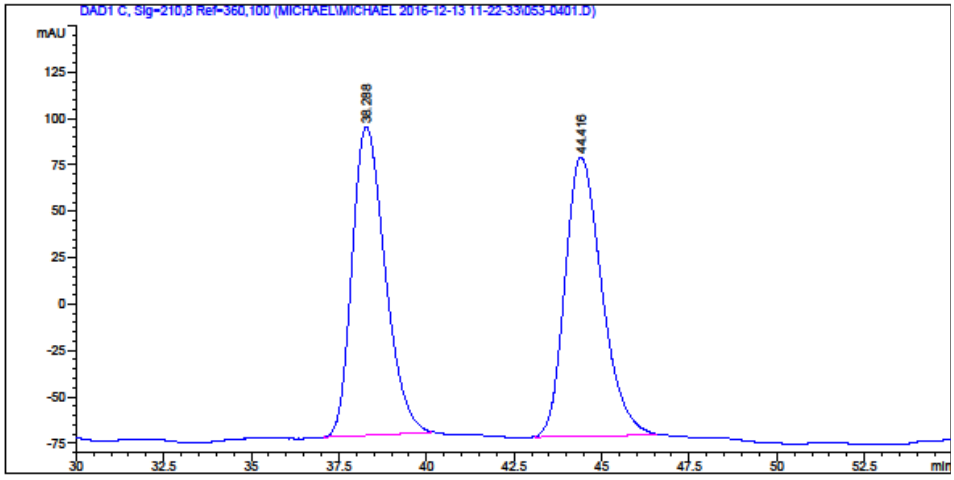
HPLC: (Chiralcel column AS-H, Hexane:2-PrOH = 99:1, 1.0 mL/min, 210 nm) ee = 90%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +16.3 (c = 1.0, $CHCl_3$).

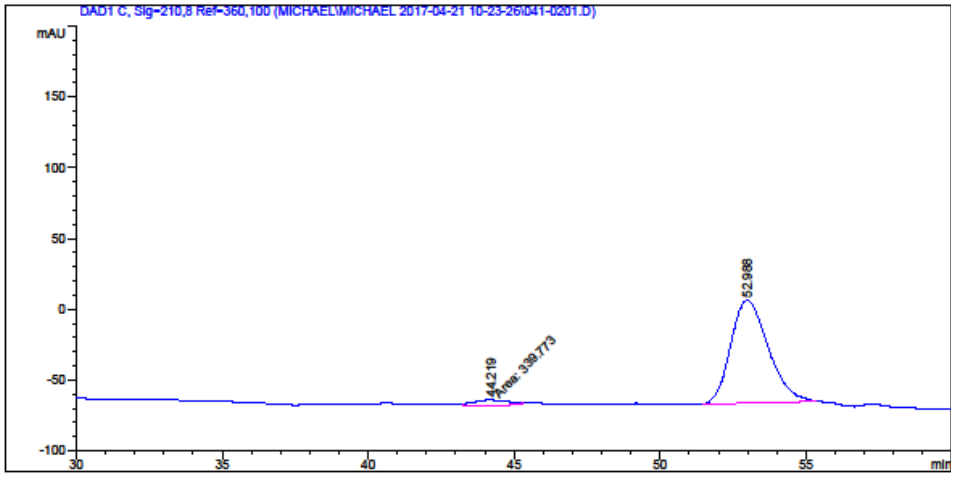

MTH-2-118diox-charac.10.fid
OH
CF3
O
O
2.2f
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-118diox-charac.11.fid
148.06
147.62
134.05
130.07
128.22
127.80
125.54
123.27
122.88
120.67
109.77
108.30
101.49
63.64
56.91
56.73
OH
CF3
O
O
2.2f
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-118diox-charac.12.fid
-69.16
OH
CF3
O
O
2.2f
19F (470 MHz, CDCl3)
f1 (ppm)

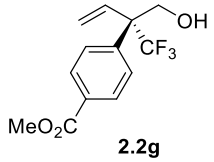


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.288	BB	0.9694	1.08323e4	165.98625	49.7445
2	44.416	BB	1.1084	1.09436e4	150.48399	50.2555



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.219	MM	1.4516	339.77313	3.90118	5.0244
2	52.988	BB	1.1659	6422.68701	72.33642	94.9756

Methyl (*S*)-4-(1,1,1-trifluoro-2-(hydroxymethyl)but-3-en-2-yl)benzoate (2.2g)



2.2g

Trifluoromethylallene **2.1g** (36.3 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (200 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 30:70 EtOAc/hexanes), the title compound **2.2g** (24.2 mg, 0.089 mmol) was obtained as a light yellow oil in 59% yield.

R_f = 0.23 (30:70 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 6.13 (dd, *J* = 10.4, 17.4 Hz, 1H), 5.63 (d, *J* = 10.4 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 4.29 (dd, *J* = 7.5, 11.8 Hz, 1H), 4.17 (dd, *J* = 7.5, 11.7 Hz, 1H), 3.92 (s, 3H), 1.63 (t, *J* = 7.4 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 139.9, 133.6, 130.2, 129.7, 129.4, 126.5 (q, *J* = 284 Hz), 121.4, 63.5, 57.3 (q, *J* = 23 Hz), 52.4.

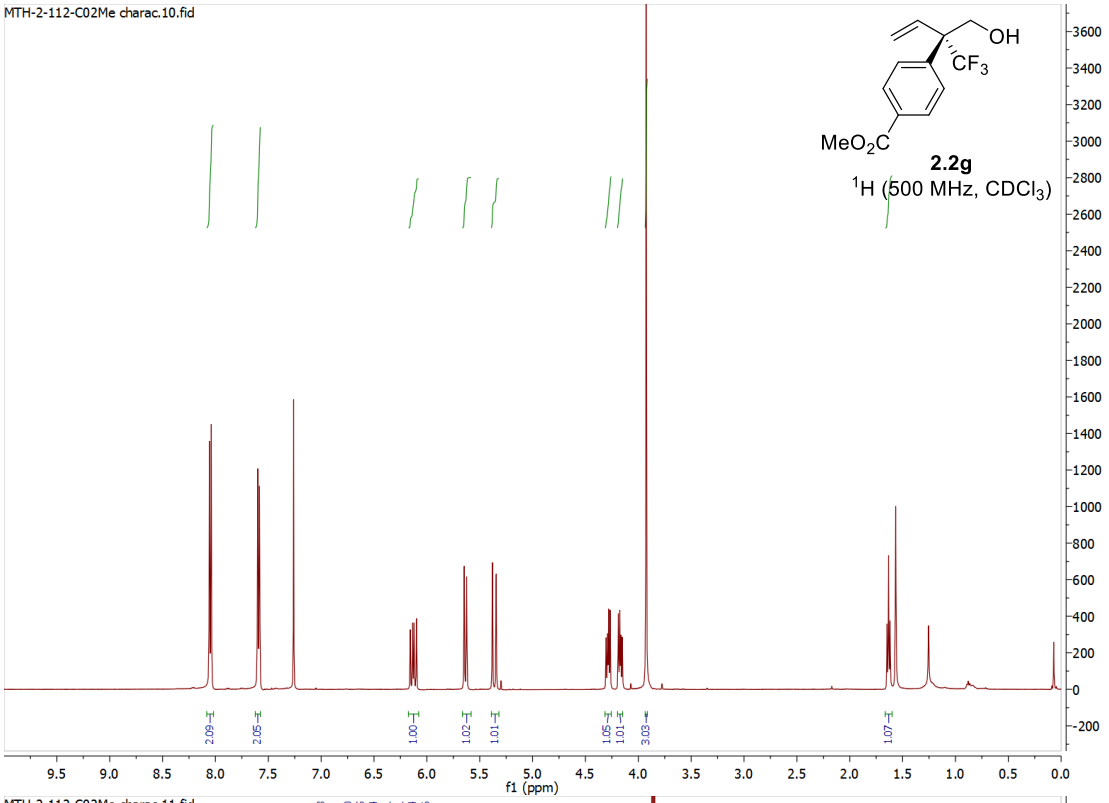
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.7.

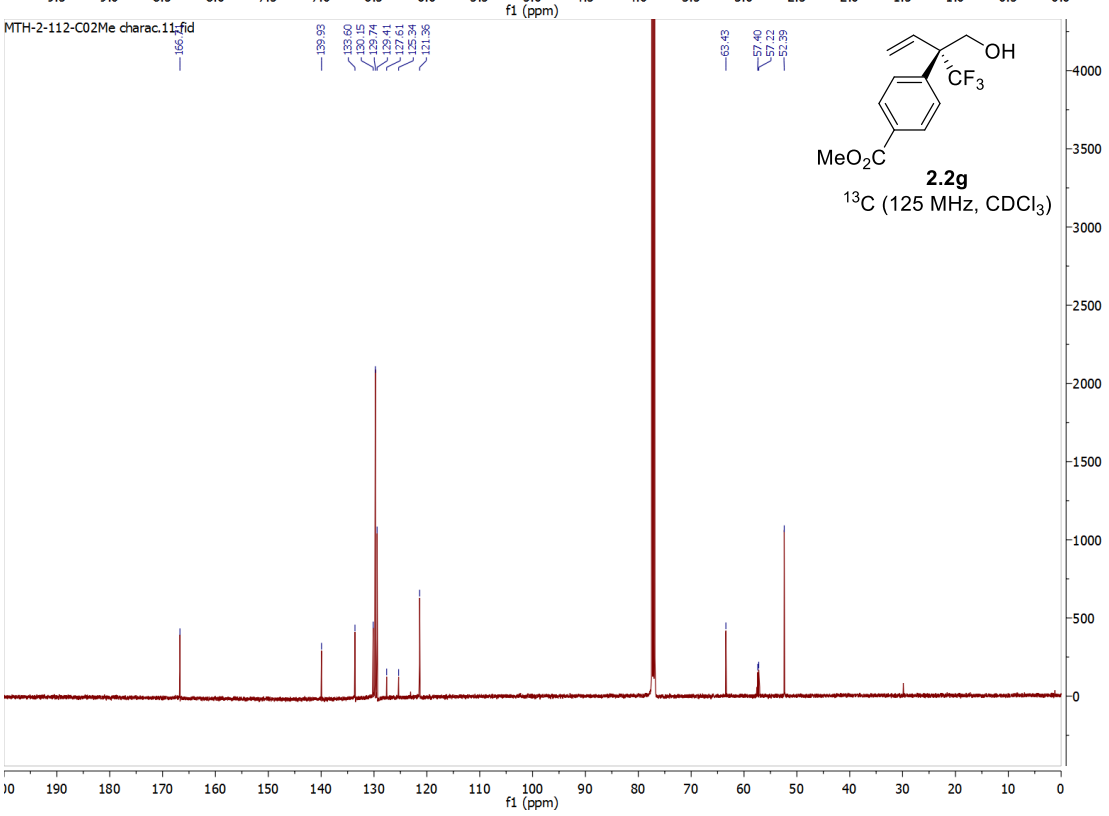
HRMS (CI+, *m/z*) for $C_{13}H_{14}O_3F_3$: calcd. = 275.0895; found = 275.0902.

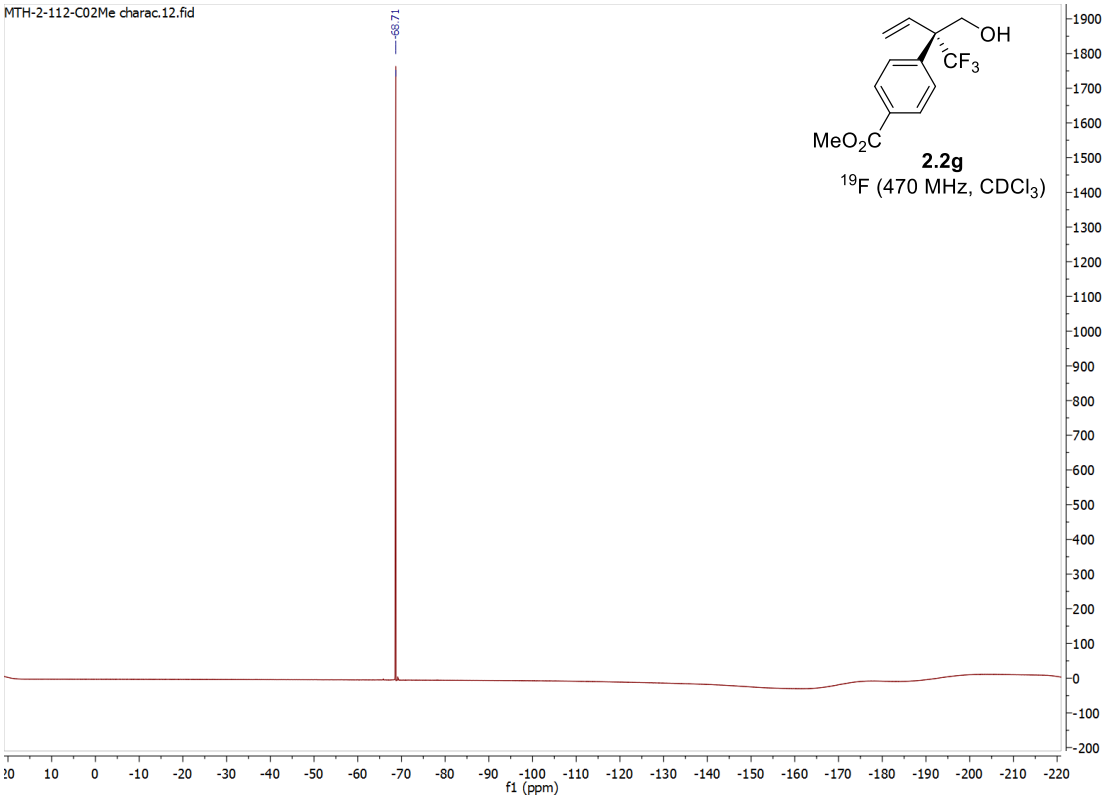
FTIR (neat): 3504, 2955, 2359, 2342, 1724, 1438, 1286, 1154, 1117, 1019, 773, 735 cm^{-1}.

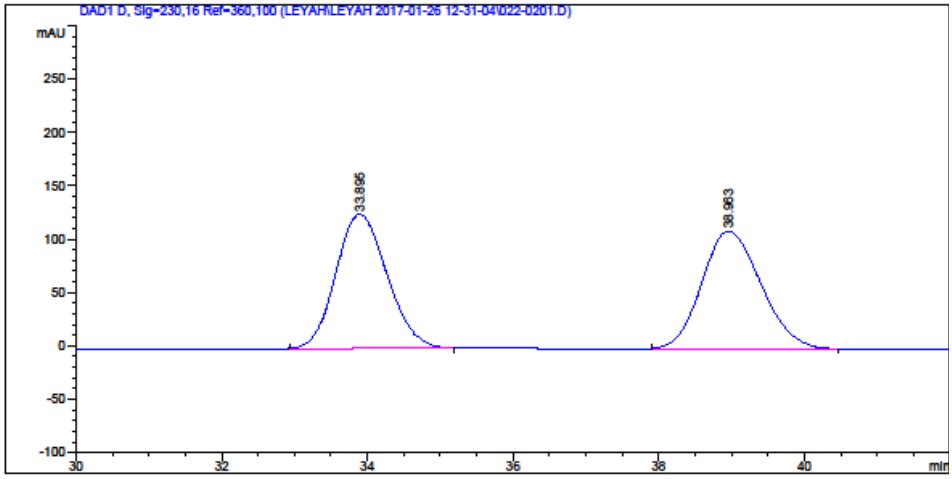
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 230 nm) ee = 92%.

$[\alpha]_D^{27}$ = +21.3 (c = 1.0, $CHCl_3$).

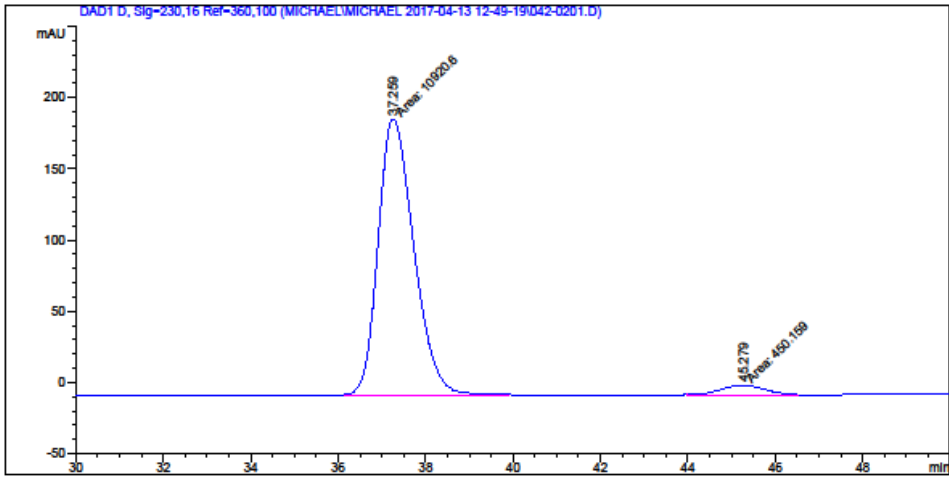

MTH-2-112-C02Me charac.10.fid
OH
CF3
MeO2C
2.2g
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-112-C02Me charac.11.fid
OH
CF3
MeO2C
2.2g
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-112-C02Me charac.12.fid
-68.71
OH
CF3
MeO2C
2.2g
19F (470 MHz, CDCl3)
f1 (ppm)

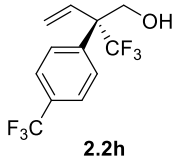


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.057	BV	0.0716	26.44418	5.54850	0.2095
2	3.148	VB	0.1042	198.84882	25.70869	1.5752
3	4.479	BB	0.1015	6.81384	1.02581	0.0540
4	5.837	BV	0.1290	14.15898	1.73801	0.1122
5	8.773	BB	0.1633	25.96805	2.45751	0.2057
6	10.736	BB	0.2476	80.99339	5.09253	0.6416
7	33.895	BB	0.7599	6083.47510	125.41604	48.1902



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.259	MM	0.9396	1.09206e4	193.70518	96.0411
2	45.279	MM	1.1033	450.15939	6.80037	3.9589

(*S*)-2-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (2.2h)



2.2h

Trifluoromethylallene **2.1h** (37.8 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (200 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.2h** (27.2 mg, 0.096 mmol) was obtained as a light yellow oil in 64% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2h** in 54% yield.

R_f = 0.31 (20:80 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (br s, 4H), 6.13 (dd, *J* = 11.4, 17.6 Hz, 1H), 5.65 (d, *J* = 11.4 Hz, 1H), 5.36 (d, *J* = 17.6 Hz, 1H), 4.29 (dd, *J* = 7.4, 12.2 Hz, 1H), 4.16 (dd, *J* = 7.0, 12.2 Hz, 1H), 1.64 (t, *J* = 7.0 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.0, 133.5, 130.6 (q, *J* = 32 Hz), 129.9, 126.4 (q, *J* = 283 Hz), 125.5 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 270 Hz), 120.8, 63.3, 57.2 (q, *J* = 23 Hz).

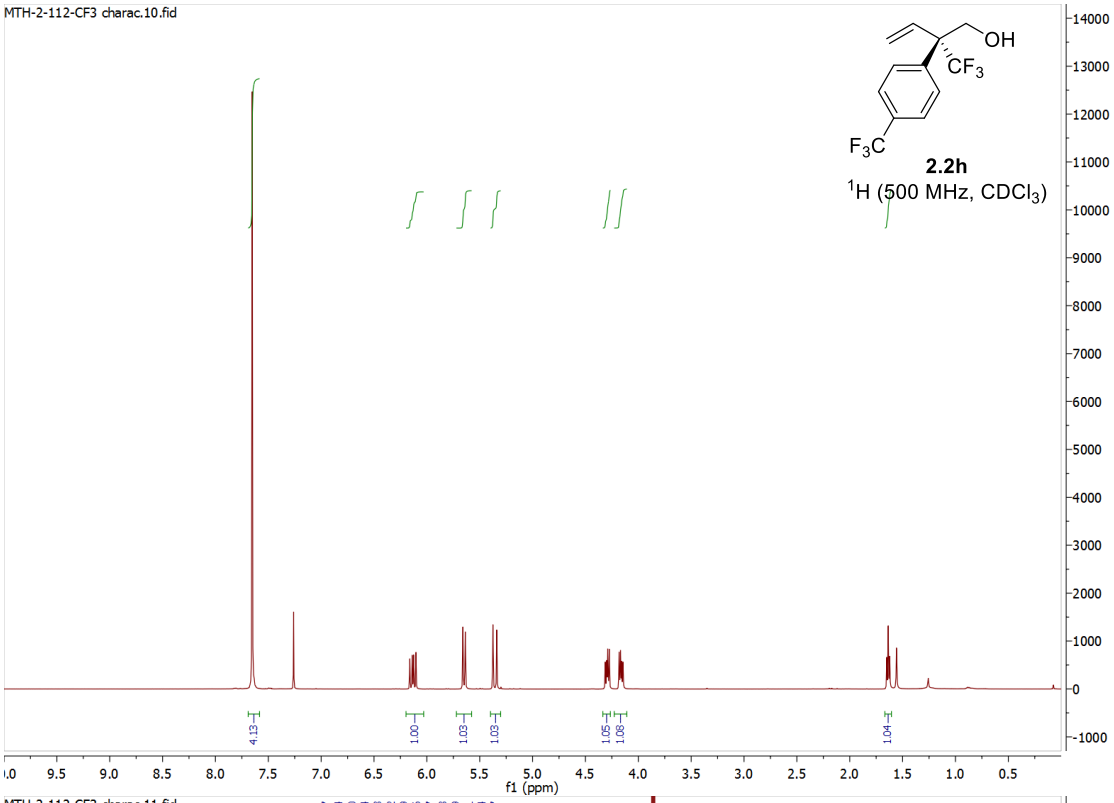
^{19}F NMR (470 MHz, $CDCl_3$) δ: -62.9, -68.9.

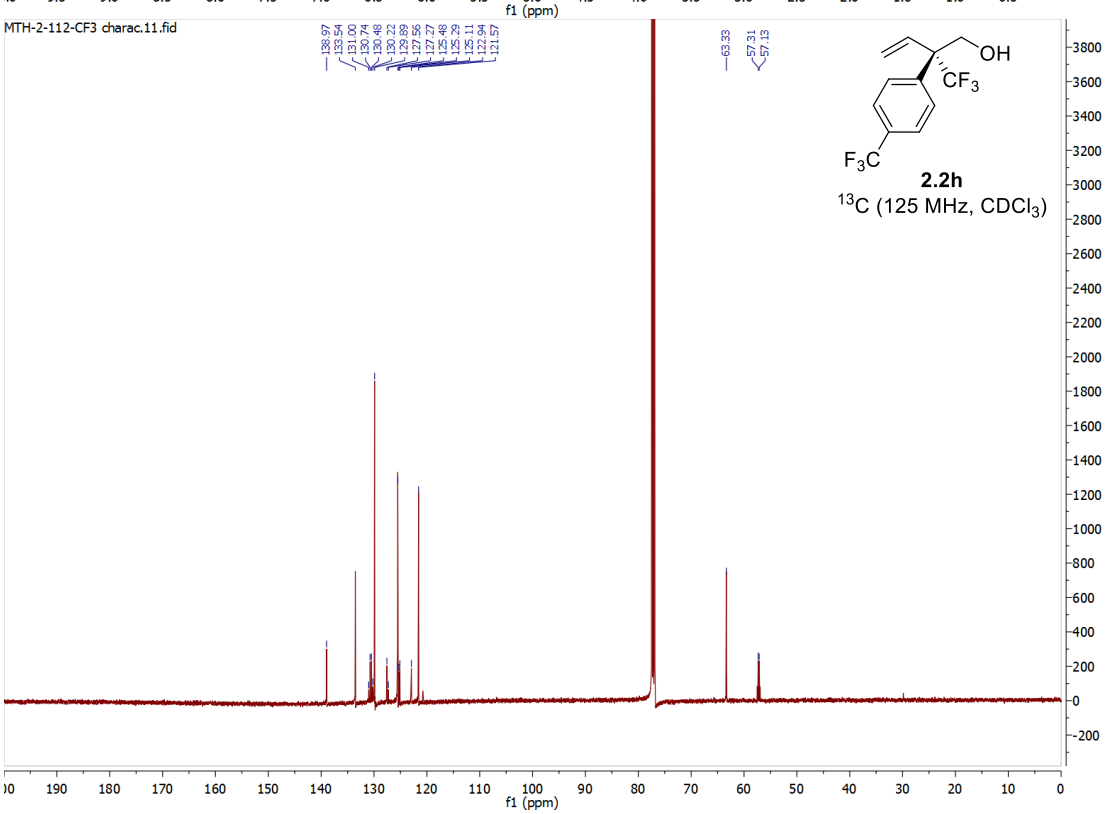
HRMS (CI+, *m/z*) for $C_{12}H_{10}OF_6$: calcd. = 284.0636; found = 284.0628.

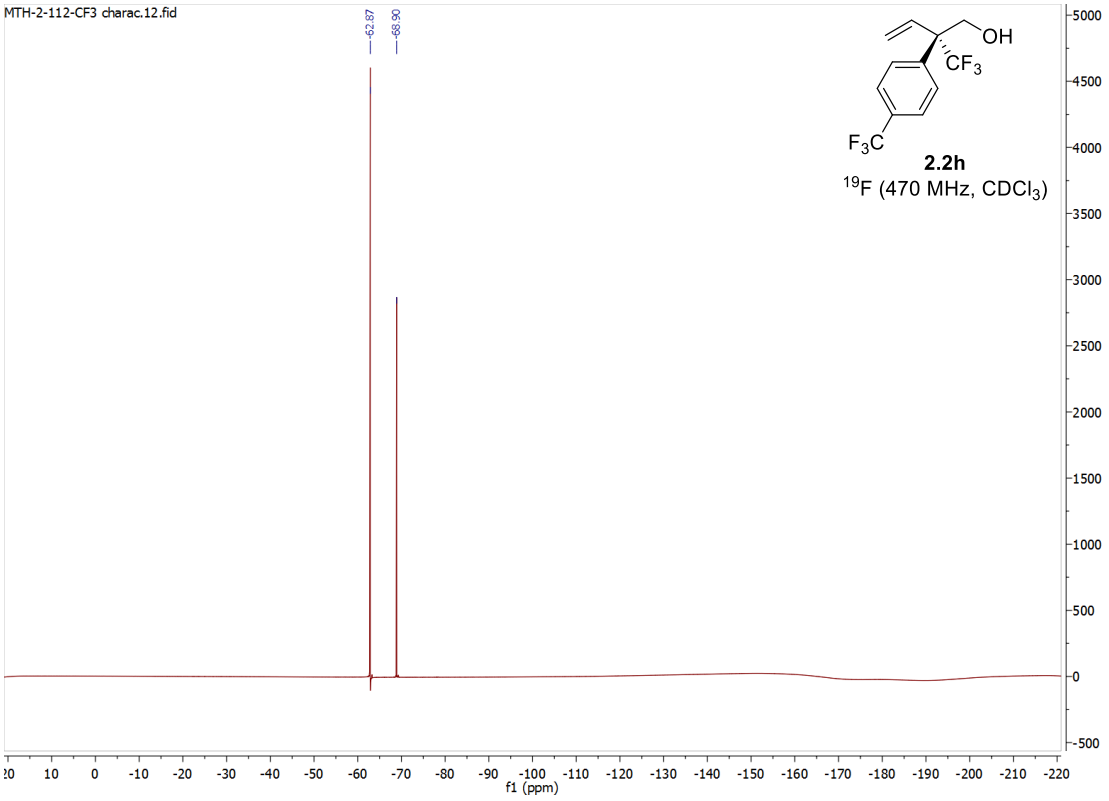
FTIR (neat): 3398, 2954, 2357, 1622, 1326, 1157, 1123, 1072, 1018, 940, 834, 731 cm^{-1}.

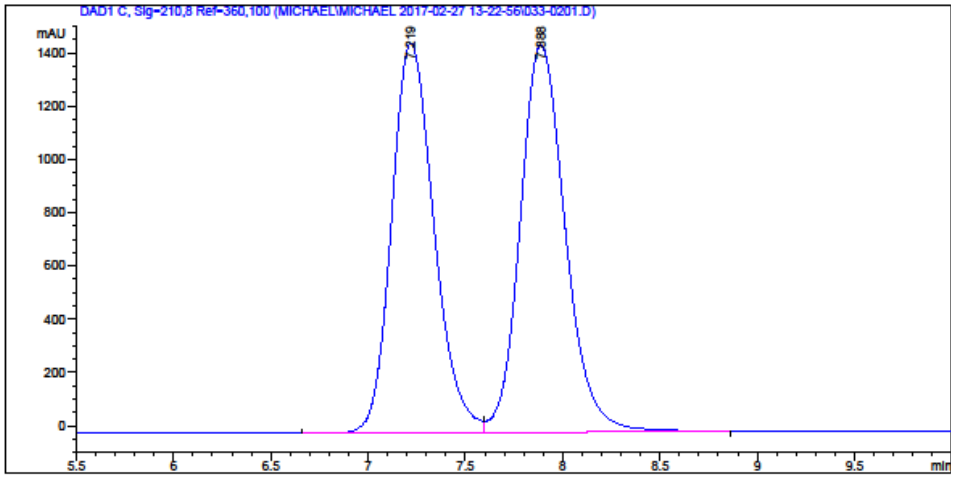
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 90% (200 mol% H_2O or 91% (500 mol% H_2O).

$[\alpha]_D^{27}$ = +4.0(c = 0.6, $CHCl_3$).

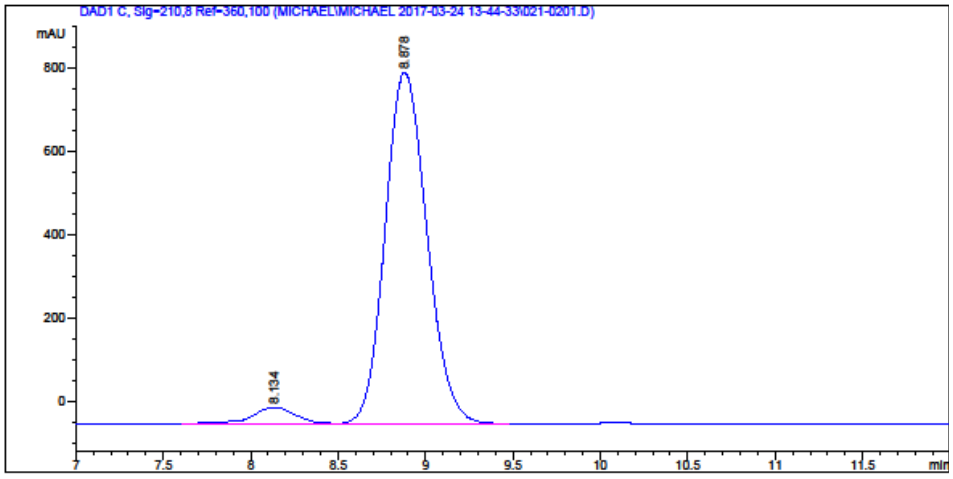

MTH-2-112-CF3 charac.10.fid
OH
CF3
F3C
2.2h
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-112-CF3 charac.11.fid
OH
CF3
F3C
2.2h
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-112-CF3 charac.12.fid
-62.87
-68.90
OH
CF3
F3C
2.2h
19F (470 MHz, CDCl3)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

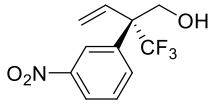


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.219	VV	0.2341	2.20711e4	1462.16272	48.6221
2	7.888	VB	0.2470	2.33221e4	1455.34534	51.3779



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.134	BV	0.2540	660.14374	39.29708	4.5214
2	8.878	VB	0.2570	1.39404e4	842.81458	95.4786

(*S*)-2-(3-nitrophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2i)



2.2i

Trifluoromethylallene **2.1i** (34.4 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (500 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 30:70 EtOAc/hexanes), the title compound **2.2i** (28.1 mg, 0.096 mmol) was obtained as a yellow oil in 72% yield. The addition of H_2O (200 mol%) afforded the title compound **2.2i** in 76% yield.

R_f = 0.29 (30:70 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.42 (s, 1H), 8.23 (d, *J* = 9.5 Hz, 1H), 7.88 (d, *J* = 9.5 Hz, 1H), 7.59 (t, *J* = 9.5 Hz, 1H), 6.16 (dd, *J* = 11.2, 17.6 Hz, 1H), 5.69 (d, *J* = 11.2 Hz, 1H), 5.36 (d, *J* = 17.6 Hz, 1H), 4.34 (dd, *J* = 7.0, 11.9 Hz, 1H), 4.18 (dd, *J* = 6.1, 11.9 Hz, 1H), 1.60 (br t, *J* = 7.0 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.5, 137.2, 135.7, 133.2, 129.5, 126.3 (q, *J* = 288 Hz), 124.8, 123.5, 122.0, 63.1, 57.1 (q, *J* = 23.6 Hz).

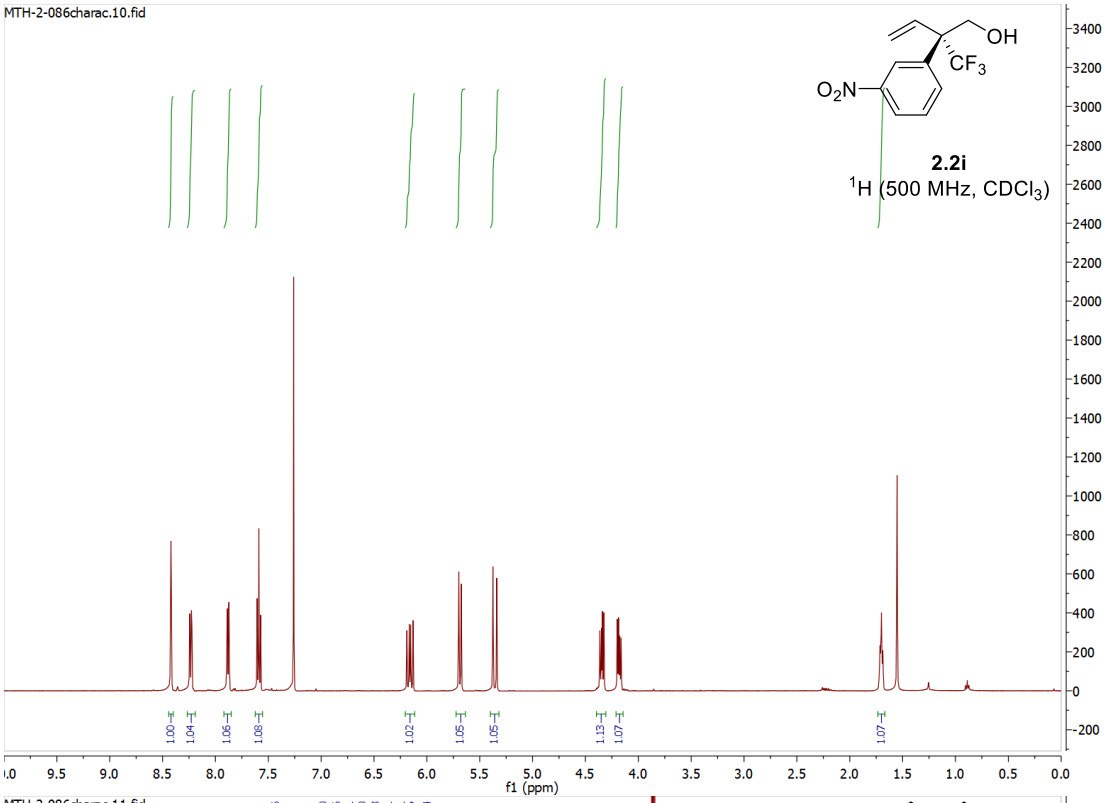
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.2.

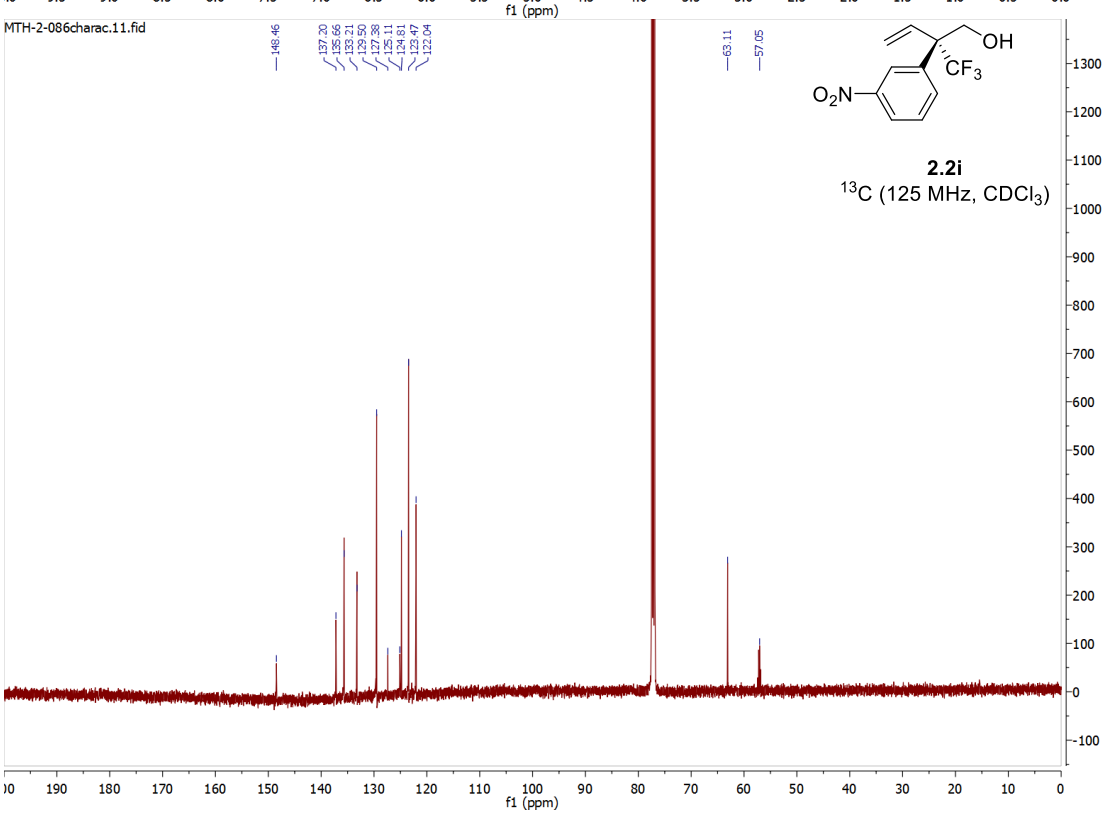
HRMS (CI+, *m/z*) for $C_{11}H_{10}NO_3F_3$ = 261.0613; found = 261.0611.

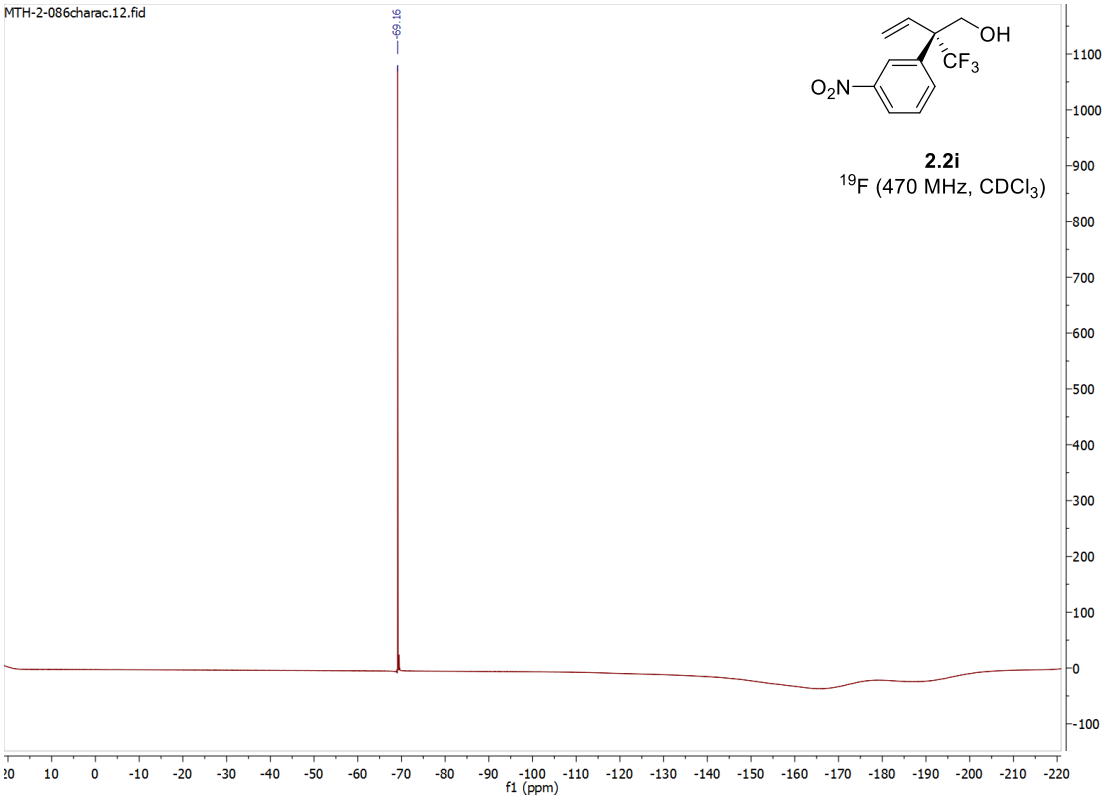
FTIR (neat): 3481, 2971, 1530, 1351, 1158, 944, 808, 739 cm^{-1}.

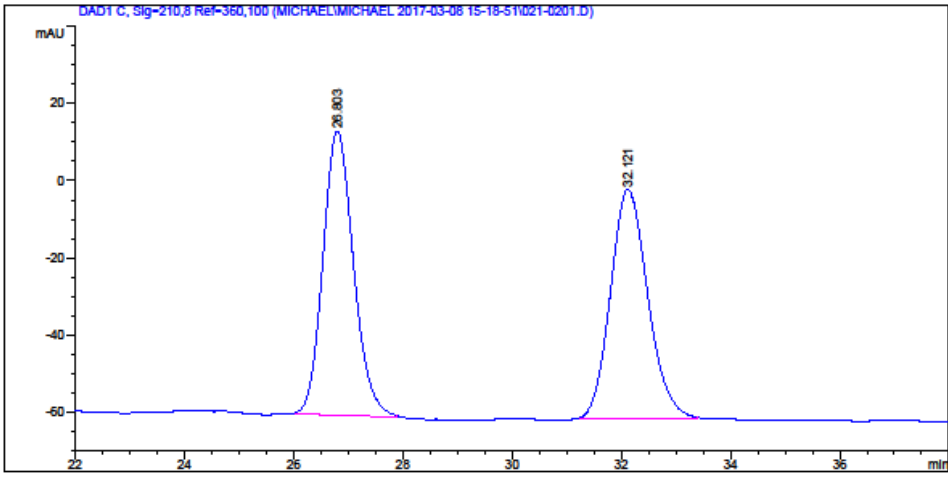
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 91% (200 mol% H_2O or 94% (500 mol% H_2O).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +31.0 (c = 1.0, $CHCl_3$).

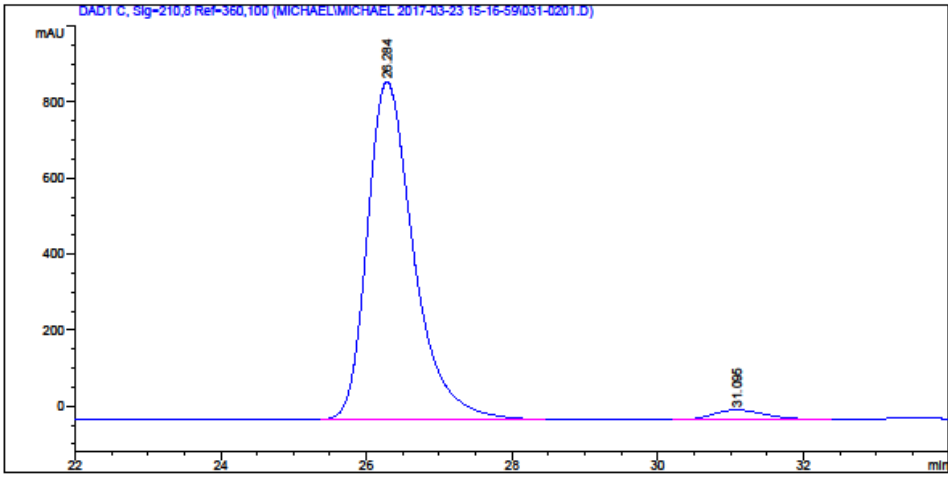

MTH-2-086charac.10.fid
OH
CF3
O2N
2.2i
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-086charac.11.fid
148.46
137.20
135.66
133.21
129.50
127.38
125.11
124.81
123.47
122.04
63.11
57.05
OH
CF3
O2N
2.2i
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-086charac.12.fid
-69.16
OH
CF3
O2N
2.2i
19F (470 MHz, CDCl3)
f1 (ppm)

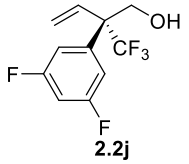


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.803	BB	0.5946	2835.67725	73.42742	50.2699
2	32.121	BB	0.7118	2805.23315	59.31419	49.7301



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.284	BB	0.6674	3.90754e4	888.01813	96.8531
2	31.095	BB	0.7027	1269.60730	25.42095	3.1469

(*S*)-2-(3,5-difluorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2j)



2.2j

Trifluoromethylallene **2.1j** (33.0 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (200 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 30:70 EtOAc/hexanes), the title compound **2.2j** (26.1 mg, 0.10 mmol) was obtained as a yellow oil in 69% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2j** in 52% yield.

R_f = 0.25 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (br d, *J* = 7.5 Hz, 2H), 6.82 (tt, *J* = 2.5, 8.0 Hz, 1H), 6.07 (dd, *J* = 11.3, 17.9 Hz, 1H), 5.64 (d, *J* = 11.3 Hz, 1H), 5.39 (d, *J* = 17.9 Hz, 1H), 4.21 (dd, *J* = 6.5, 11.7 Hz, 1H), 4.11 (dd, *J* = 6.5, 11.7 Hz, 1H), 1.65 (t, *J* = 6.5 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0 (dd, *J* = 16.4, 254 Hz), 138.8 (t, *J* = 8.6 Hz), 133.0, 126.3 (q, *J* = 286 Hz), 122.8, 112.7 (m), 104.1 (t, *J* = 26.7 Hz), 63.4 (q, *J* = 2.0 Hz), 57.0 (q, *J* = 21.1 Hz).

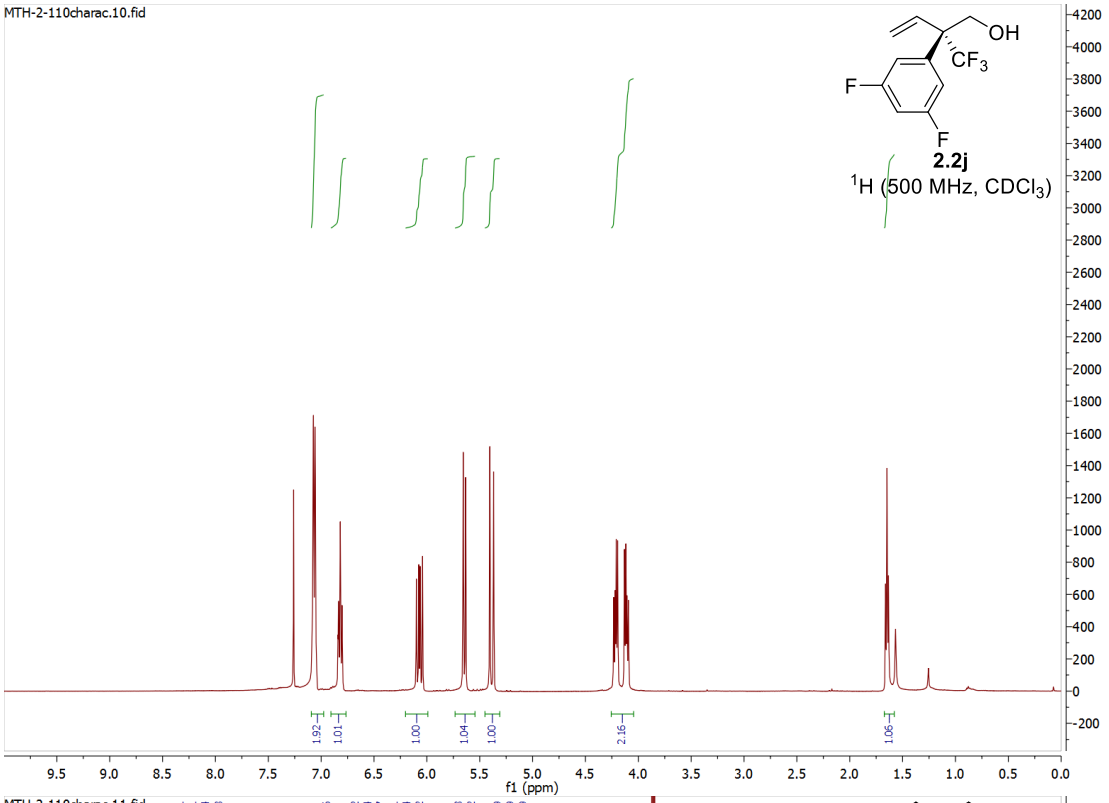
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.9, -108.9 (t, *J* = 8.8 Hz).

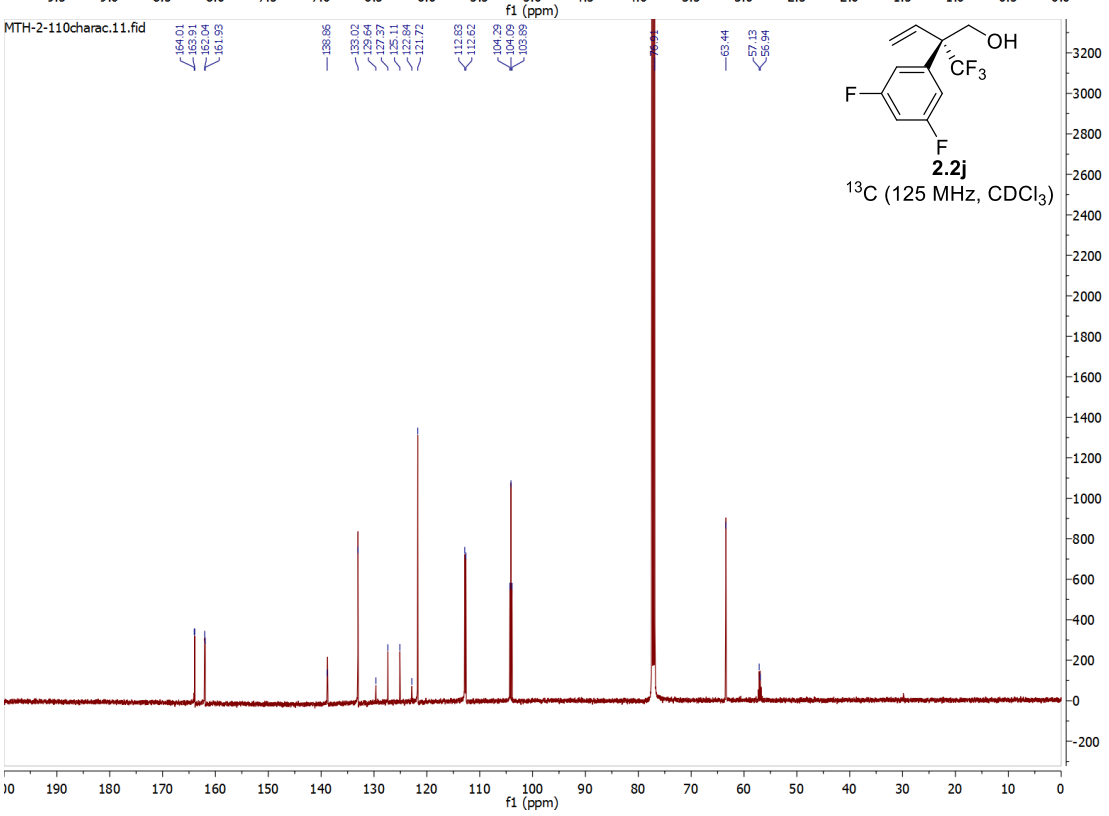
HRMS (CI+, *m/z*) for $C_{11}H_9OF_5$: calcd. = 252.0574; found = 252.0575.

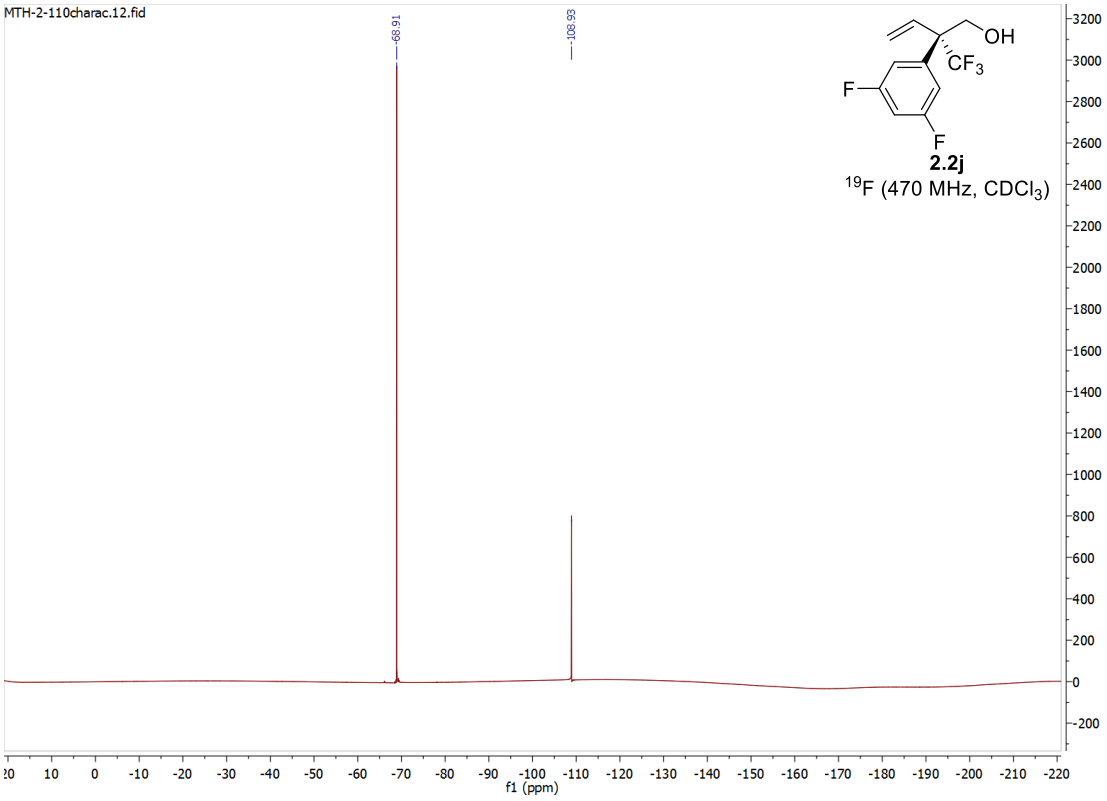
FTIR (neat): 3409, 2957, 2359, 1626, 1601, 1438, 1172, 1121, 987, 857 cm^{-1}.

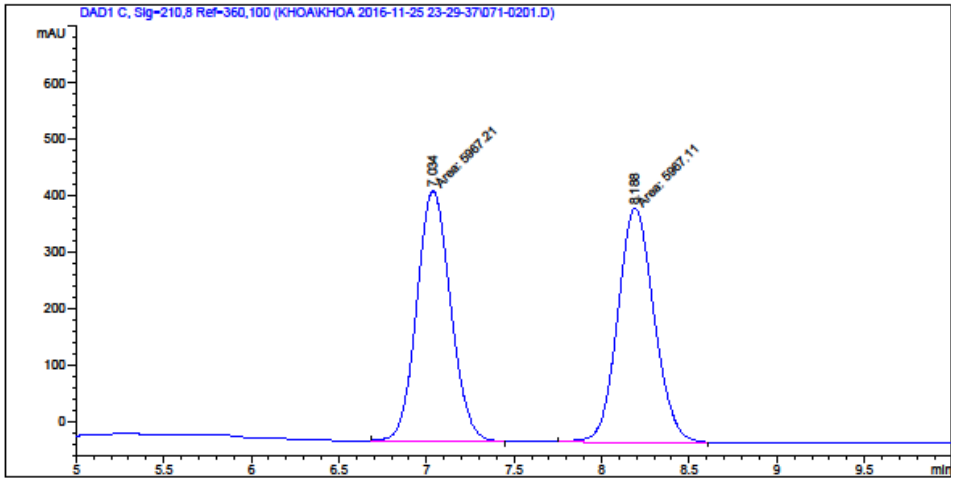
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 91% (200 mol% H_2O or 93% (500 mol% H_2O).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +24.2 (c = 1.0, $CHCl_3$).

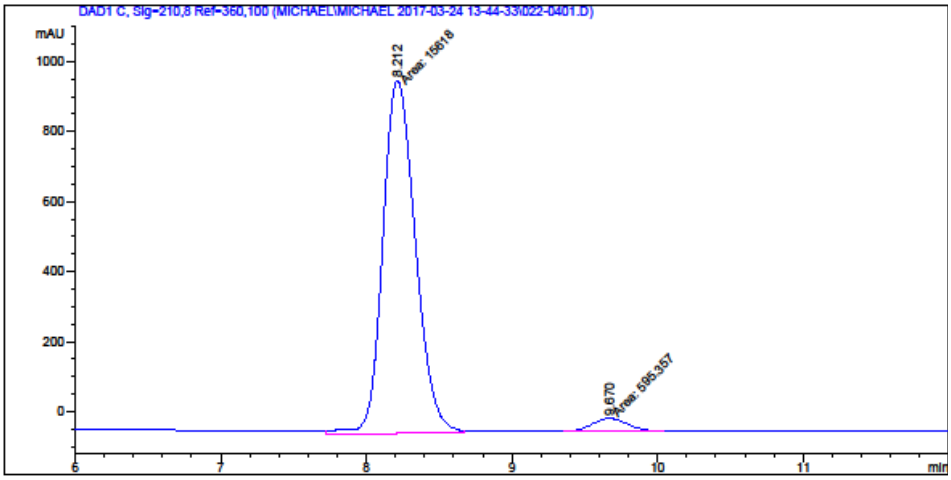

MTH-2-110charac.10.fid
OH
CF3
F
F
2.2j
1H (500 MHz, CDCl3)
1.92
1.01
1.00
1.04
1.00
2.16
1.06
f1 (ppm)


MTH-2-110charac.11.fid
164.01
163.91
162.04
161.93
138.86
133.02
129.64
127.37
125.11
122.84
121.72
112.83
112.62
104.29
104.09
103.89
77.61
63.44
57.13
56.94
OH
CF3
F
F
2.2j
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-110charac.12.fid
-68.91
-108.93
OH
CF3
F
F
2.2j
19F (470 MHz, CDCl3)
f1 (ppm)

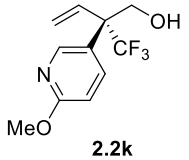


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.034	MM	0.2234	5967.20996	445.18460	50.0004
2	8.188	MM	0.2403	5967.11279	413.94617	49.9996



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.212	MM	0.2582	1.56180e4	1008.01666	96.3280
2	9.670	MM	0.2726	595.35748	36.39767	3.6720

(*S*)-2-(6-methoxypyridin-3-yl)-2-(trifluoromethyl)but-3-en-1-ol (2.2k)



2.2k

Trifluoromethylallene **2.1k** (32.5 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C. Upon flash column chromatography (SiO_2, 25:75 EtOAc/hexanes), the title compound **2.2k** (29.7 mg, 0.12 mmol) was obtained as a yellow oil in 80% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2k** in 71% yield.

R_f = 0.23 (1:3 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 2.7 Hz, 1H), 7.69 (dd, *J* = 2.7, 8.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.11 (dd, *J* = 11.8. 18.5 Hz, 1H), 5.63 (d, *J* = d, *J* = 11.8 Hz, 1H), 5.35 (d, *J* = 18.5 Hz, 1H), 4.24 (dd, *J* = 7.7, 12.3 Hz, 1H), 4.10 (dd, *J* = 6.9, 12.3 Hz, 1H), 3.95 (s, 3H), 1.64 (br m, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.8, 147.9, 139.5, 133.4, 126.4 (q, *J* = 276 Hz), 123.1, 121.3, 110.6, 62.8 (q, *J* = 2.8 Hz), 55.3 (q, *J* = 23.7 Hz), 53.5.

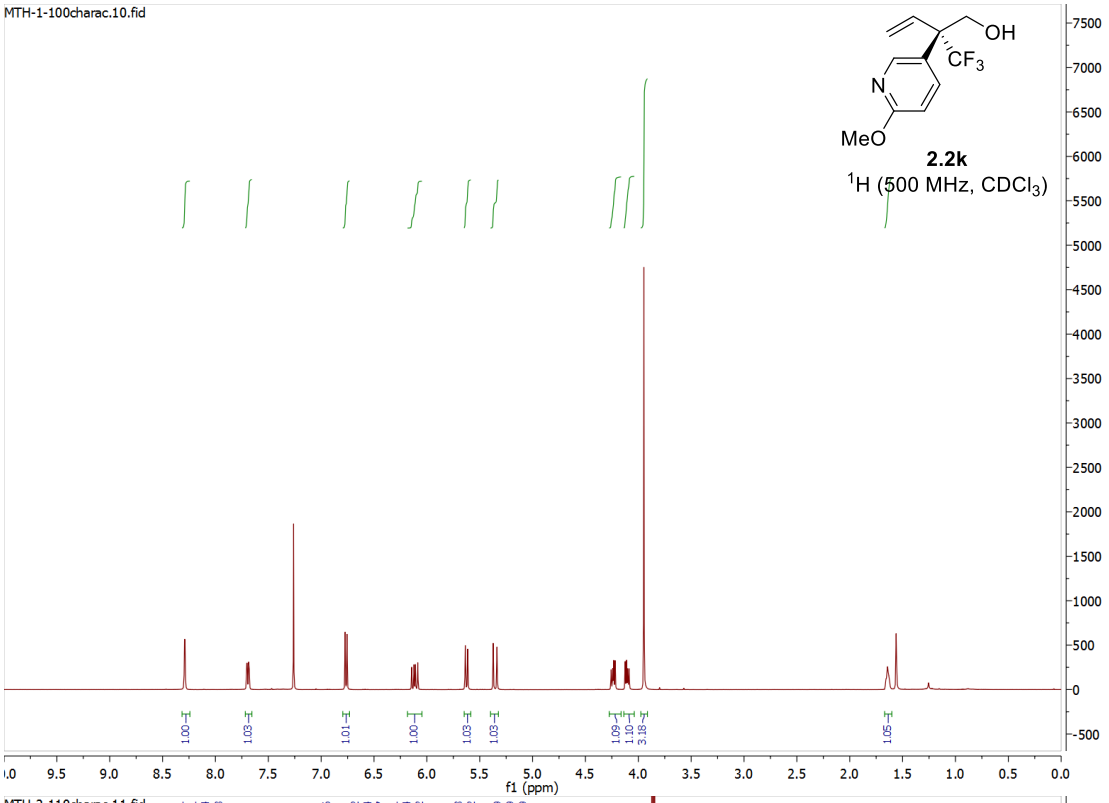
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.8.

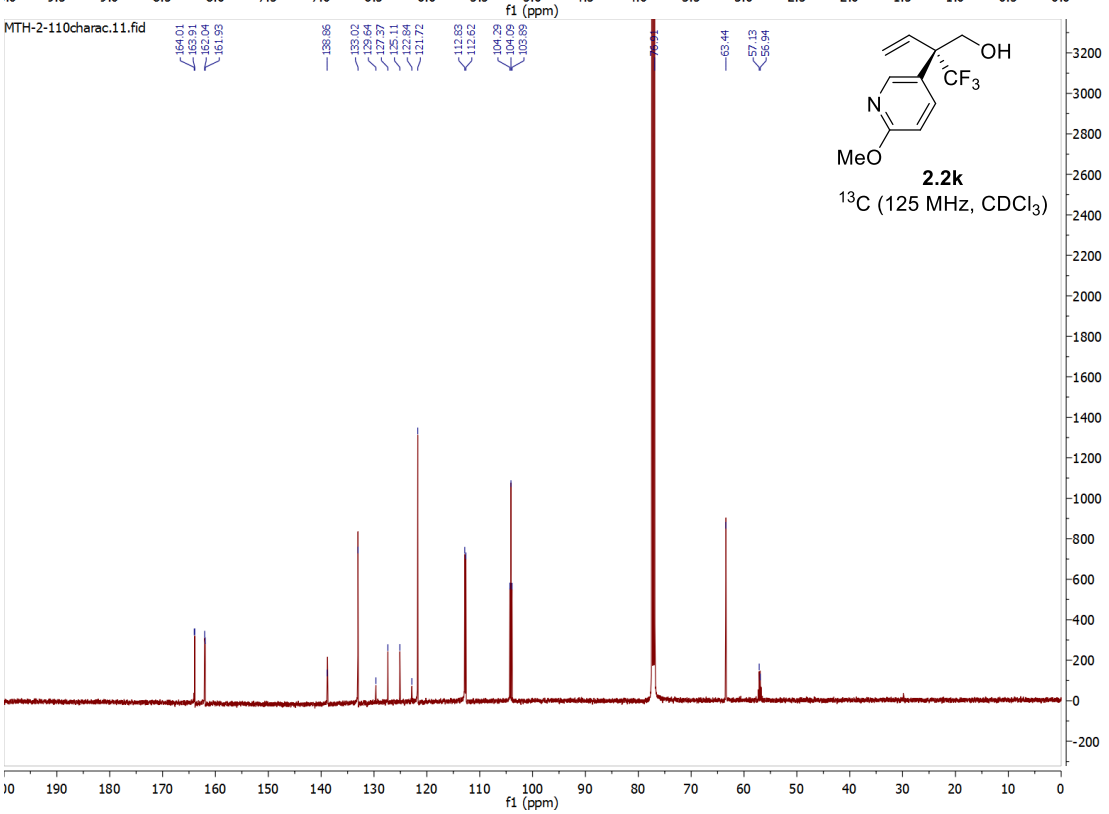
HRMS (H+, *m/z*) for $C_{11}H_{12}F_3NO_2$: 248.0893, found: 248.0893.

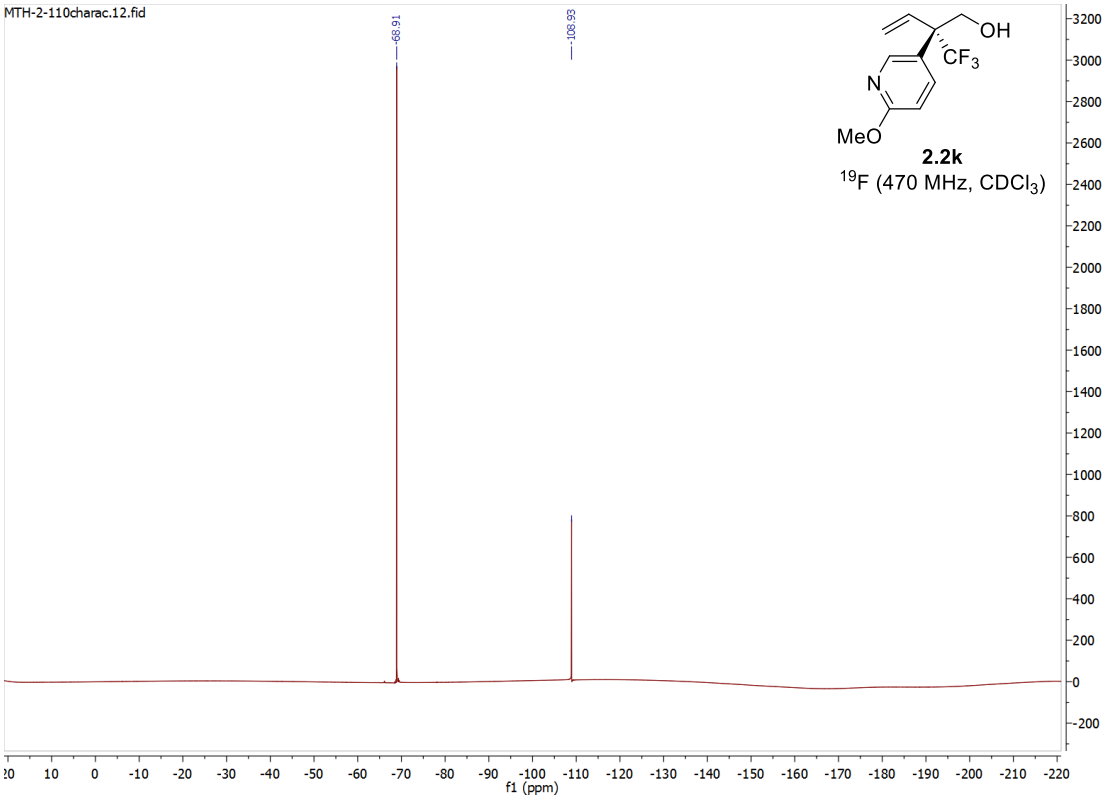
FTIR (neat): 3372, 2952, 2363, 1608, 1571, 1497, 1385, 1295, 1260, 1154, 1076, 1022, 936, 832 cm^{-1}.

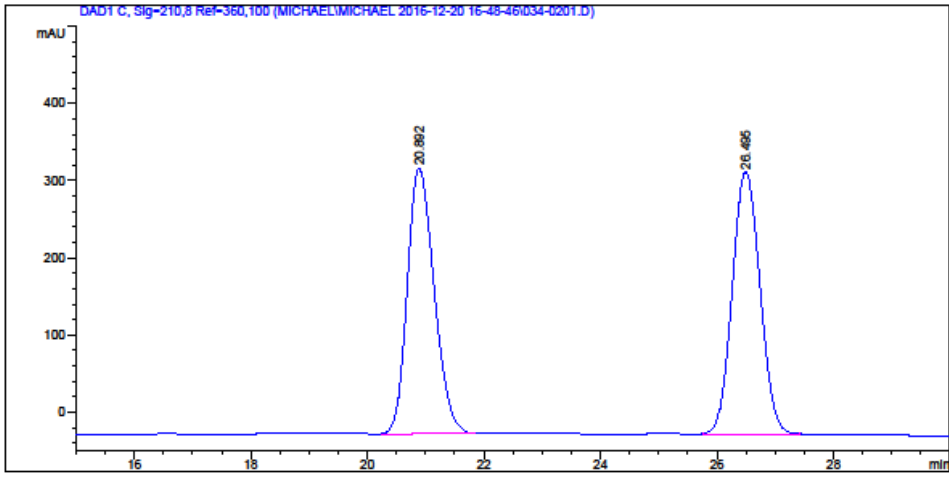
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 84% or 89% (500 mol% H_2O).

$[\alpha]_D^{27}$ = +1.5 (c = 0.78, $CHCl_3$).

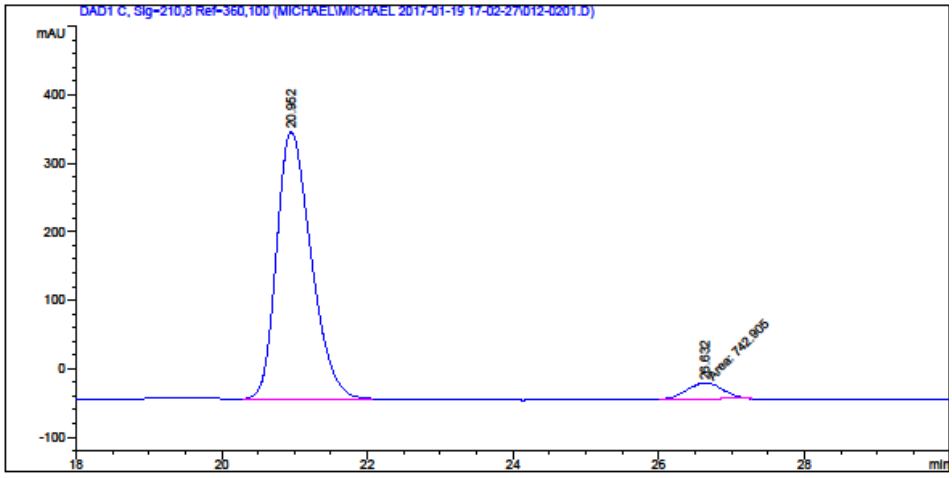

MTH-1-100charac.10.fid
OH
CF3
N
MeO
2.2k
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-2-110charac.11.fid
OH
CF3
N
MeO
2.2k
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-110charac.12.fid
-68.91
-108.93
OH
CF3
N
MeO
2.2k
19F (470 MHz, CDCl3)
f1 (ppm)

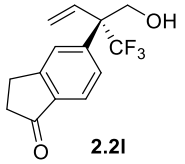


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.892	BB	0.4936	1.09509e4	343.77304	49.5451
2	26.495	BB	0.5200	1.11520e4	338.77664	50.4549



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.952	BB	0.5040	1.27611e4	389.70374	94.4986
2	26.632	MM	0.5382	742.90521	23.00651	5.5014

(*S*)-5-(1,1,1-trifluoro-2-(hydroxymethyl)but-3-en-2-yl)-2,3-dihydro-1H-inden-1-one (2.2l)



2.2l

Trifluoromethylallene **2.1l** (35.7 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (200 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 40:60 EtOAc/hexanes), the title compound **2.2l** (32.8 mg, 0.12 mmol) was obtained as a yellow oil in 81% yield. The addition of H_2O (500 mol%) afforded the title compound **2.2l** in 59% yield.

R_f = 0.24 (40:60 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.14 (dd, *J* = 10.1, 16.2 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 5.38 (d, *J* = 16.2 Hz, 1H), 4.32 (dd, *J* = 7.1, 12.0 Hz, 1H), 4.19 (dd, *J* = 6.9, 12.0 Hz, 1H), 3.17 (m, 2H), 2.71 (m, 2H), 1.70 (t, *J* = 6.7 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.6, 155.3, 141.9, 136.7, 128.6, 127.8, 126.6 (q, *J* = 288 Hz), 123.7, 121.4, 63.5, 57.5 (q, *J* = 23 Hz), 36.6, 26.1.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.5.

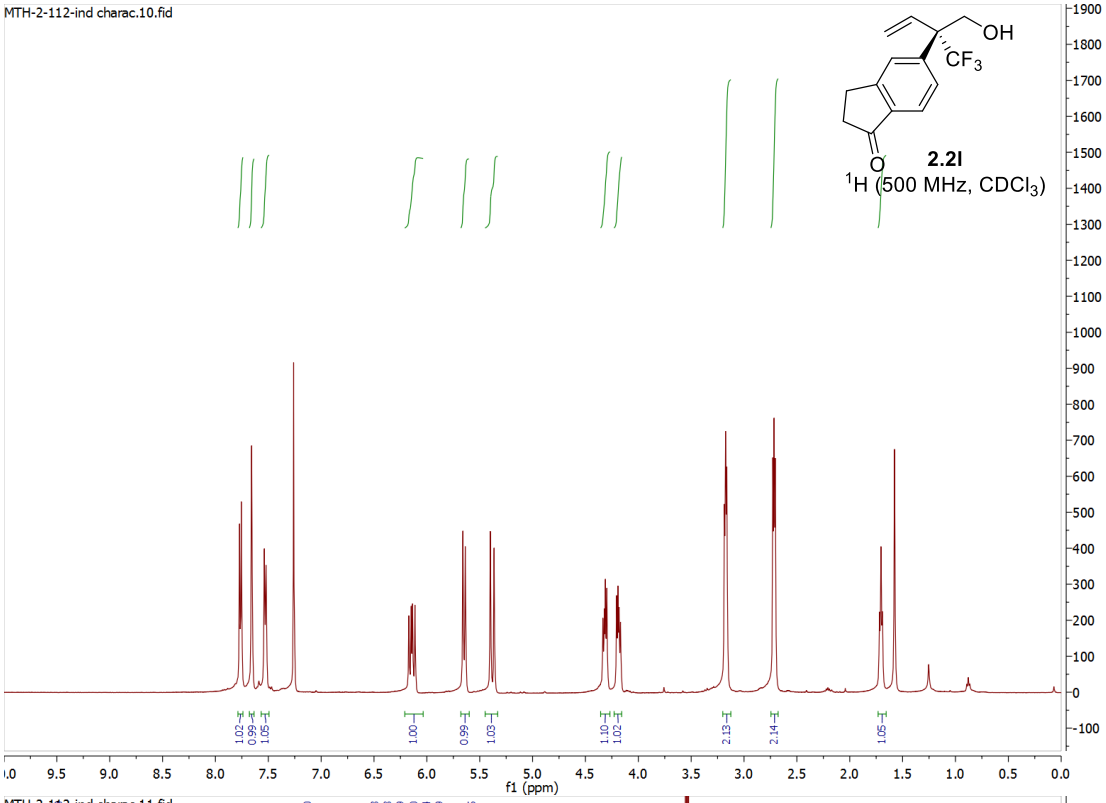
HRMS (CI+, *m/z*) for $C_{14}H_{14}O_2F_3$: calcd. = 271.0946; found = 271.0940.

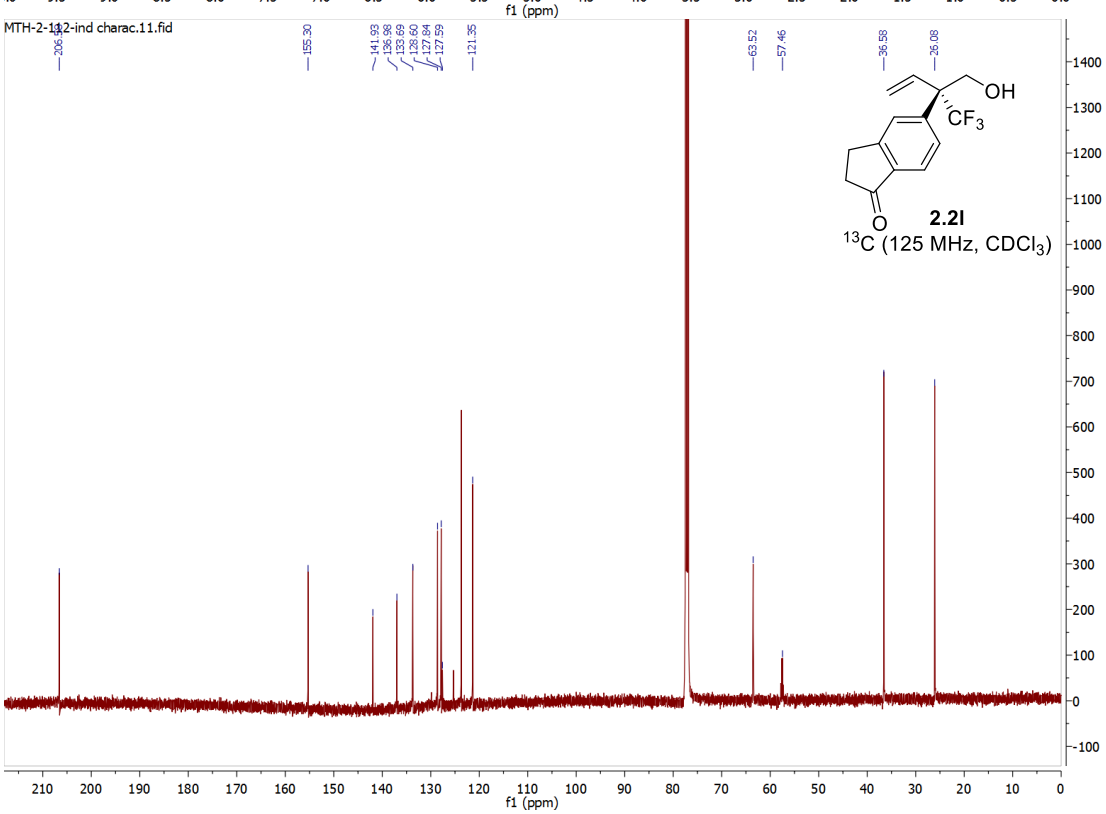
FTIR (neat): 3456, 2965, 2361, 1702, 1611, 1324, 1248, 1168, 1138, 1050 cm^{-1}.

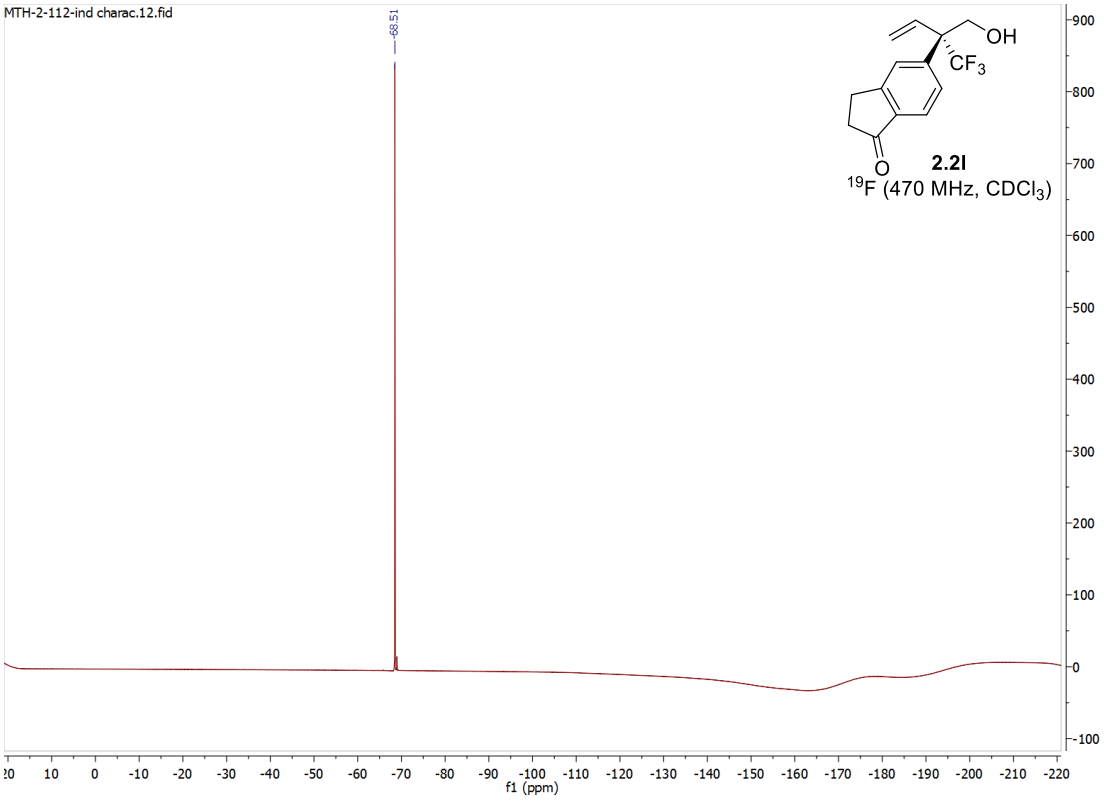
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 89% (200 mol% H_2O or 92% (500 mol% H_2O).

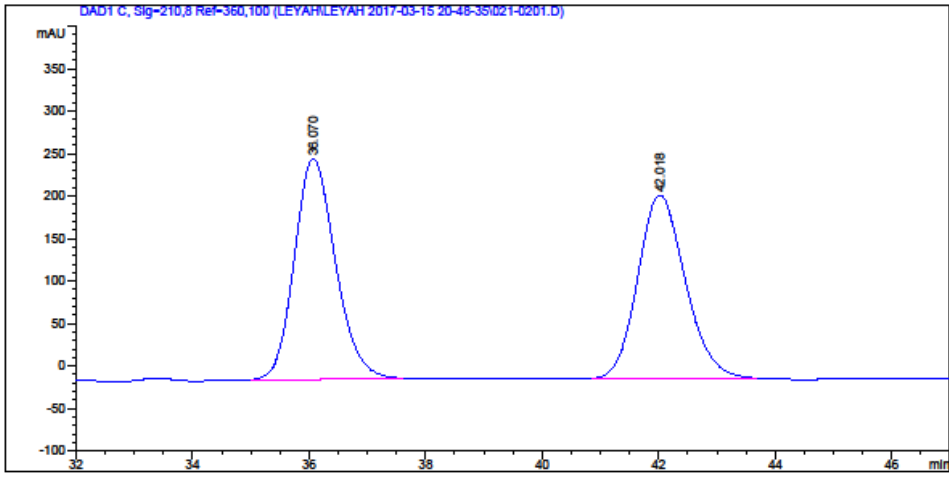
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +22.9 (c = 1.0, $CHCl_3$).

Melting Point = 69-71 °C

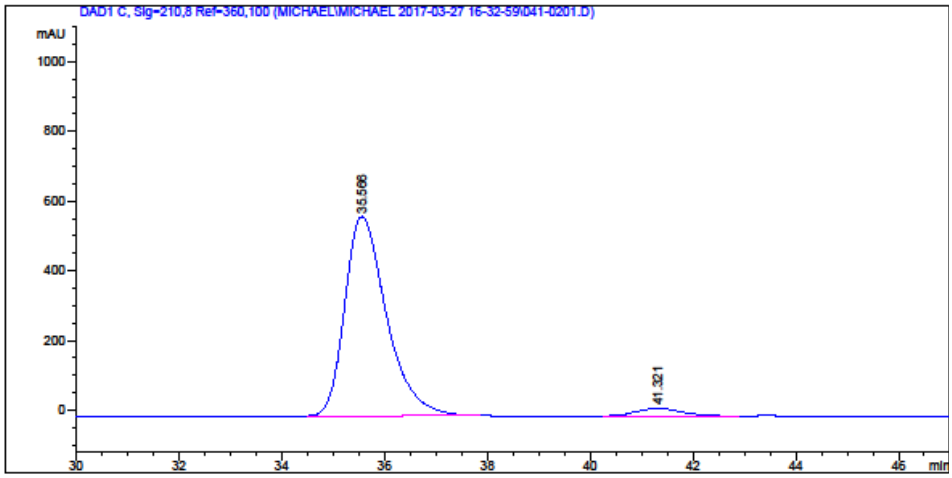

MTH-2-112-ind charac.10.fid
OH
CF3
O
2.2l
1H (500 MHz, CDCl3)
1.02
0.99
1.05
1.00
0.99
1.03
1.10
1.02
2.13
2.14
1.05
f1 (ppm)


MTH-2-112-ind charac.11.fid
206.42
155.30
141.93
136.98
133.69
128.60
127.84
127.59
121.35
63.52
57.46
36.58
26.08
OH
CF3
O
2.2l
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-112-ind charac.12.fid
-68.51
OH
CF3
O
2.2l
19F (470 MHz, CDCl3)
900
800
700
600
500
400
300
200
100
0
-100
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

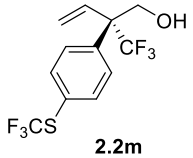


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.070	BB	0.7541	1.26616e4	259.09067	50.9977
2	42.018	BB	0.8544	1.21662e4	215.59528	49.0023



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.566	BB	0.8495	3.19110e4	571.41003	96.0937
2	41.321	BB	0.7395	1297.21704	21.39066	3.9063

(*S*)-2-(trifluoromethyl)-2-(4-((trifluoromethyl)thio)phenyl)but-3-en-1-ol (2.2m)



2.2m

Trifluoromethylallene **2.1m** (42.6 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (500 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 10:90 EtOAc/hexanes), the title compound **2.2m** (27.4 mg, 0.087 mmol) was obtained as a yellow oil in 58% yield.

R_f = 0.29 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 2H), 6.12 (dd, *J* = 9.7, 18.3 Hz, 1H), 5.64 (d, *J* = 9.7 Hz, 1H), 5.37 (d, *J* = 18.3 Hz, 1H), 4.27 (dd, *J* = 7.3, 11.8 Hz, 1H), 4.16 (dd, *J* = 7.3, 11.8 Hz, 1H), 1.61 (t, *J* = 7.3 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.0, 136.2, 133.5, 130.5, 129.5 (q, *J* = 300 Hz), 126.4 (q, *J* = 284 Hz), 124.8, 121.5, 63.4, 57.1 (q, *J* = 22.1 Hz).

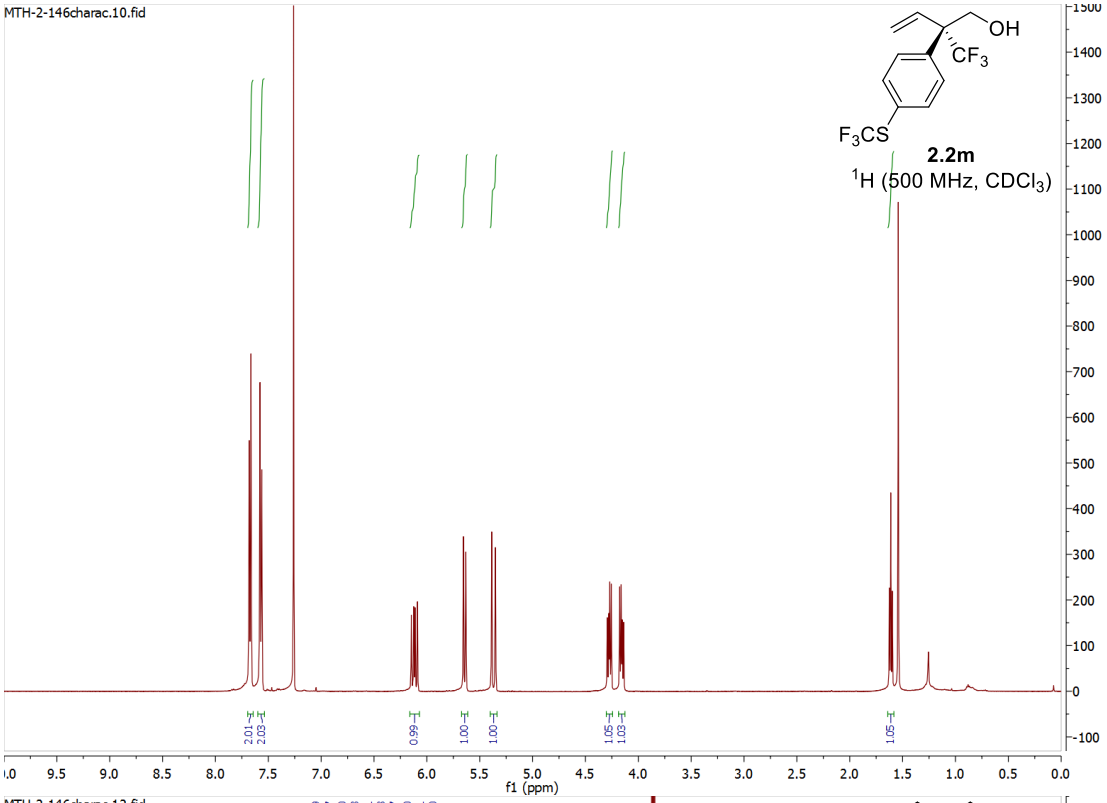
^{19}F NMR (470 MHz, $CDCl_3$) δ: -42.3, -68.8.

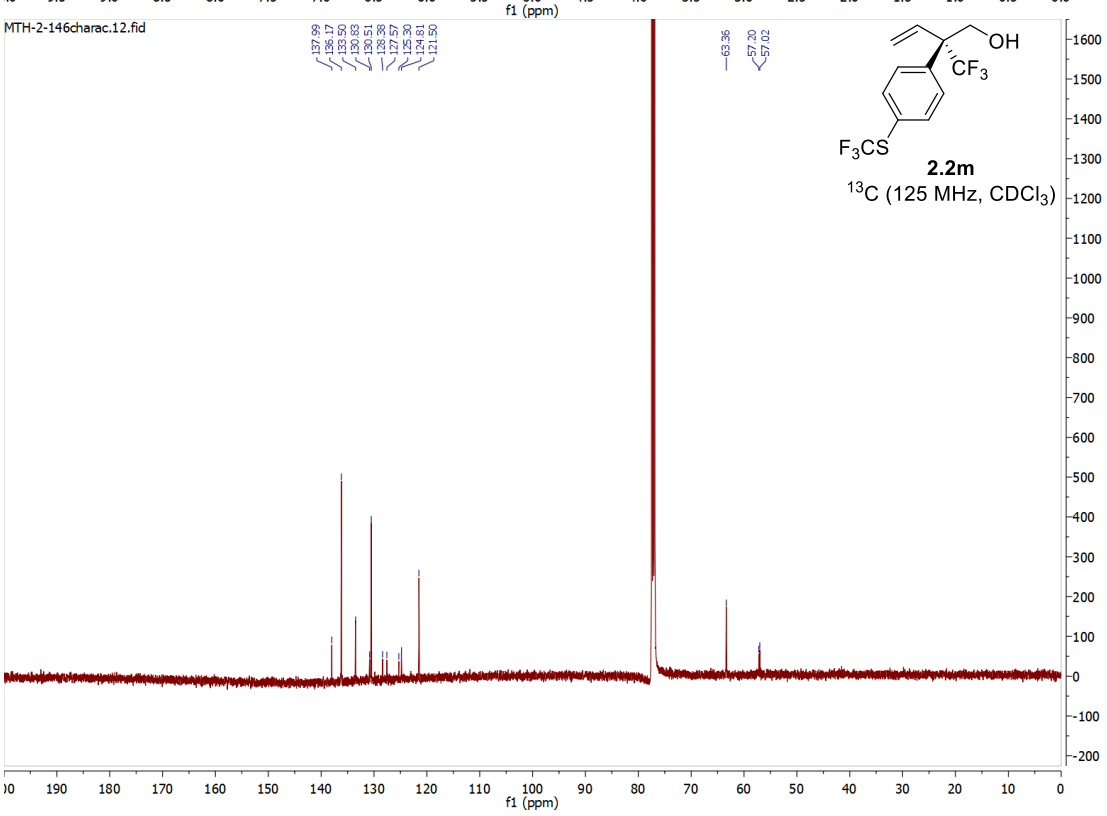
HRMS (CI+, *m/z*) for $C_{12}H_{10}OSF_6$ = 316.0357; found = 316.0354

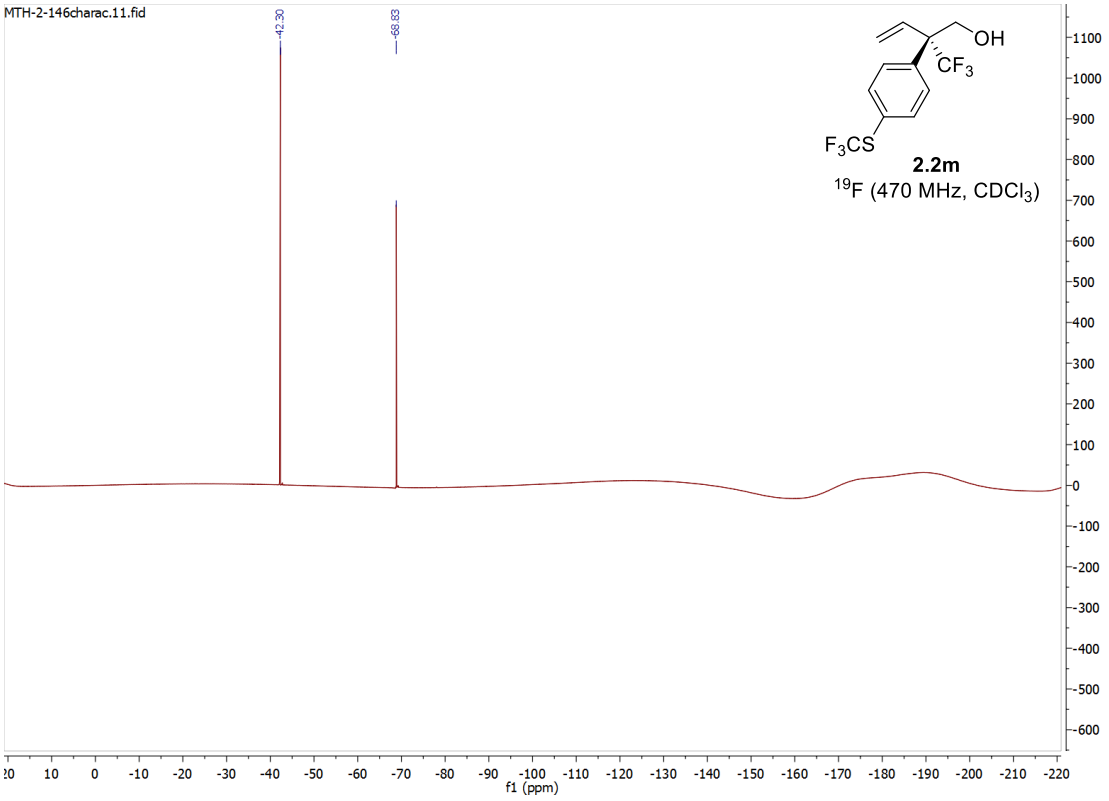
FTIR (neat): 3402, 2972, 2484, 1498, 1259, 1090, 1054, 1033, 940, 826, 757 cm^{-1}.

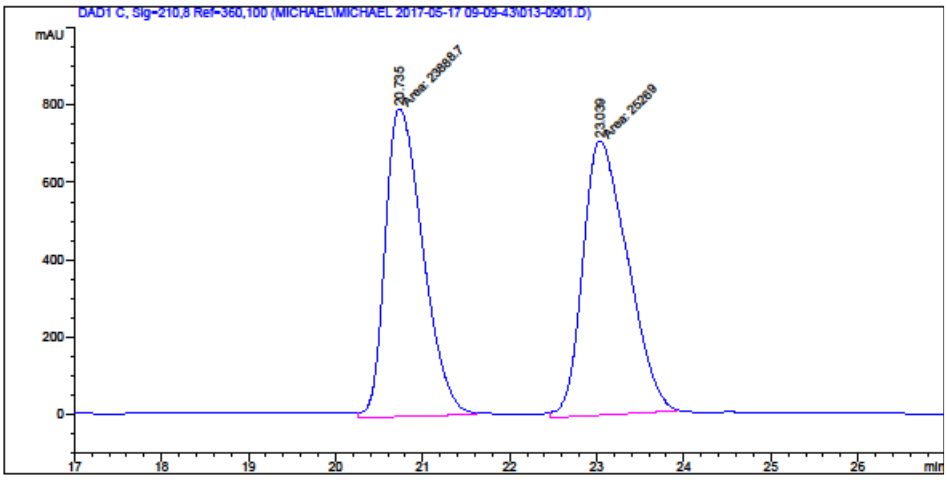
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 99:1, 1.0 mL/min, 210 nm) ee = 91%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +21.9 (c = 1.0, $CHCl_3$).

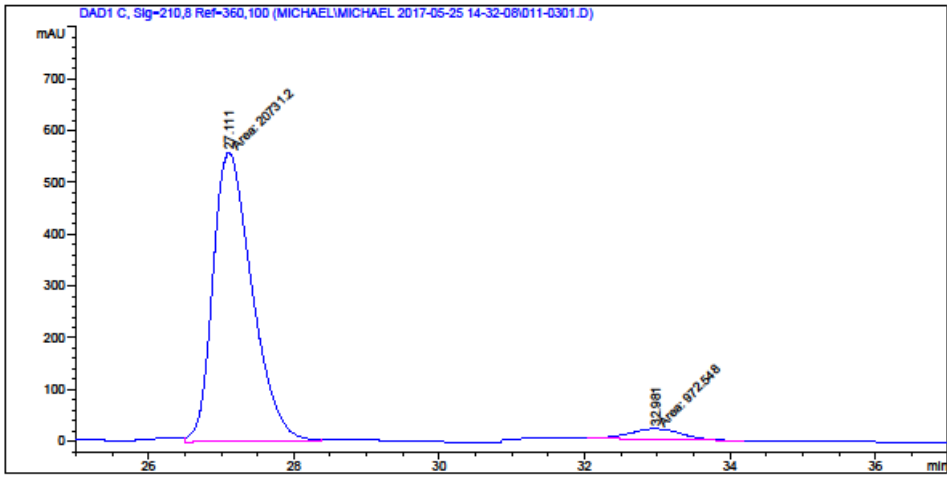

MTH-2-146charac.10.fid
OH
CF3
F3CS
2.2m
1H (500 MHz, CDCl3)
2.01
2.03
0.99
1.00
1.00
1.05
1.03
1.05
f1 (ppm)


MTH-2-146charac.12.fid
137.99
136.17
133.50
130.83
130.51
128.38
127.57
125.30
124.81
121.50
63.36
57.20
57.02
OH
CF3
F3CS
2.2m
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-146charac.11.fid
-42.30
-68.83
OH
CF3
F3CS
2.2m
19F (470 MHz, CDCl3)
f1 (ppm)

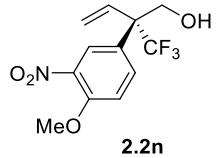


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.735	MM	0.5007	2.38887e4	795.13849	48.5961
2	23.039	MM	0.5943	2.52690e4	708.66974	51.4039



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.111	MM	0.6189	2.07312e4	558.25330	95.5190
2	32.981	MM	0.8085	972.54803	20.04895	4.4810

(*S*)-2-(4-methoxy-3-nitrophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2n)



2.2n

Trifluoromethylallene **2.1n** (38.9 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (500 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 30:70 EtOAc/hexanes), the title compound **2.2n** (32.1 mg, 0.11 mmol) was obtained as a yellow oil in 73% yield.

R_f = 0.13 (15:85 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 2.5, 8.9 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 6.11 (dd, *J* = 11.7, 17.0 Hz, 1H), 5.65 (d, *J* = 11.7 Hz, 1H), 5.35 (d, *J* = 17.0 Hz, 1H), 4.26 (dd, *J* = 7.4, 12.2 Hz, 1H), 4.11 (dd, *J* = 7.4, 12.2 Hz, 1H), 3.98 (s, 3H), 1.69 (t, *J* = 7.4 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.8, 139.5, 135.3, 133.3, 127.2, 127.1, 126.4 (q, *J* = 284 Hz), 121.8, 113.5, 63.1 (q, *J* = 2.6 Hz), 56.7, 56.4 (q, *J* = 22.8 Hz).

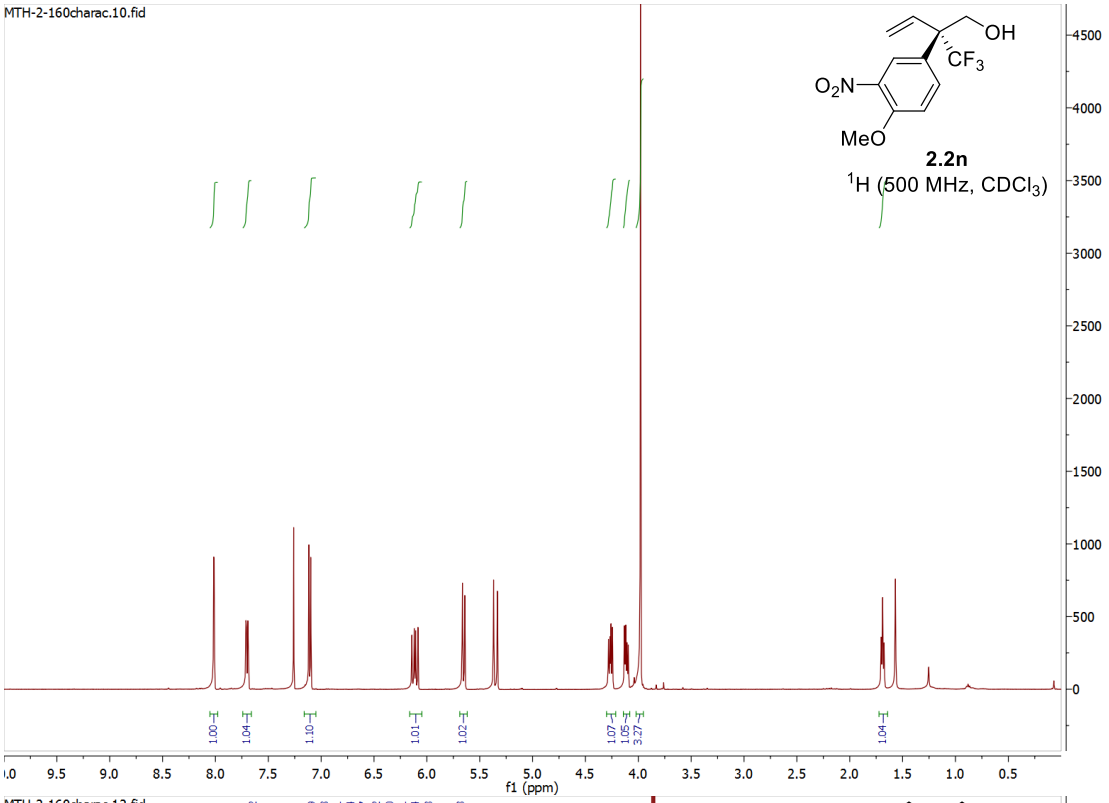
^{19}F NMR (470 MHz, $CDCl_3$) δ: -69.6.

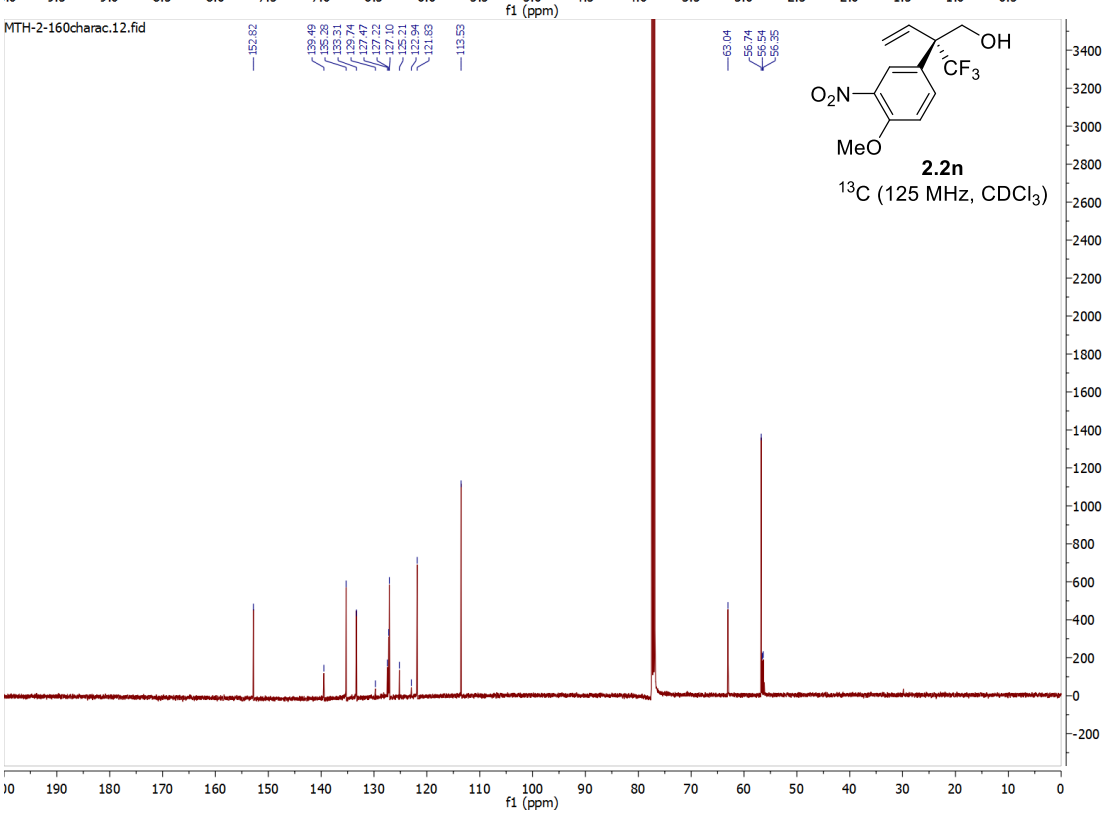
HRMS (CI+, *m/z*) for $C_{12}H_{12}NO_4F_3$ = 291.0718; found = 291.0717.

FTIR (neat): 3536, 2950, 1623, 1531, 1353, 1272, 1156, 1055, 1033, 1016, 944, 821 cm^{-1}.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 90:10, 1.0 mL/min, 210 nm) ee = 94%.

$[\alpha]_D^{27}$ = +21 (c = 1.0, $CHCl_3$).


MTH-2-160charac.10.fid
OH
CF3
O2N
MeO
2.2n
1H (500 MHz, CDCl3)
1.00
1.04
1.10
1.01
1.02
1.07
1.05
3.27
1.04
f1 (ppm)


MTH-2-160charac.12.fid
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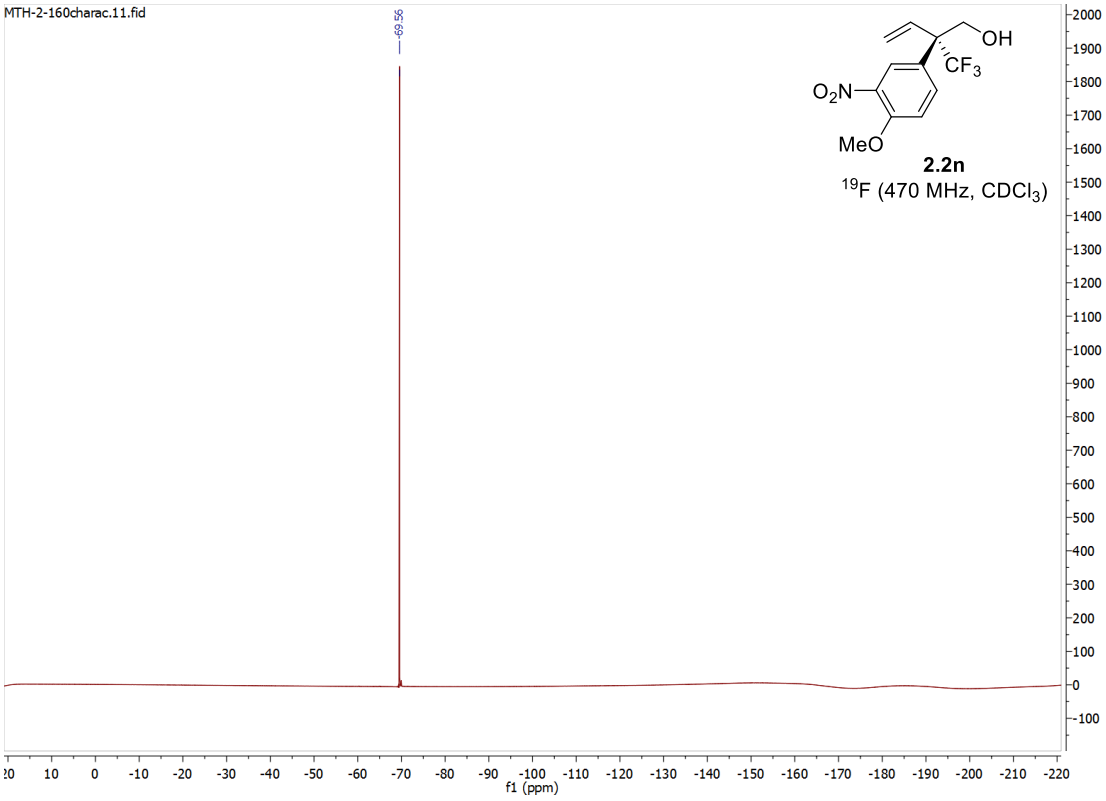
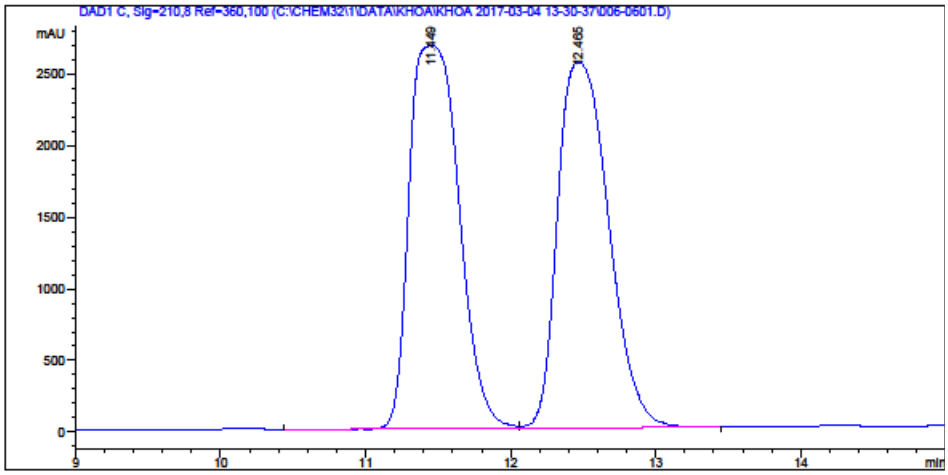
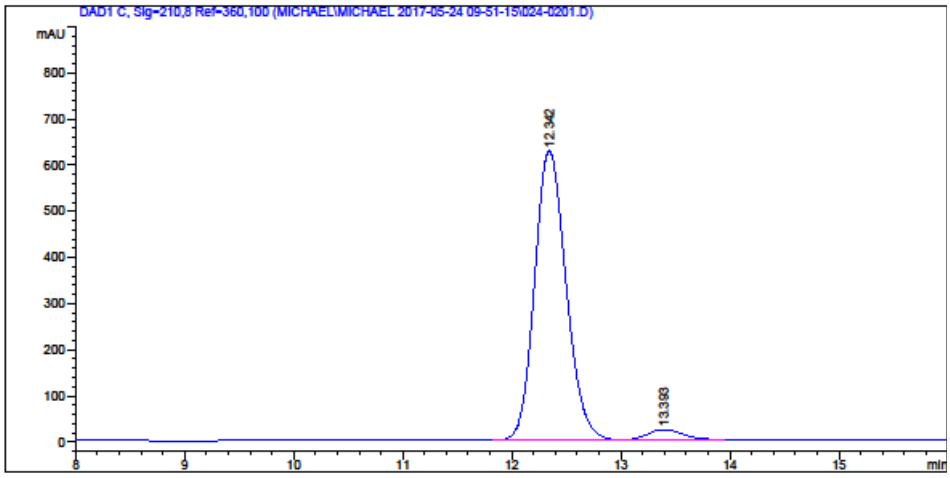
139.49
135.38
133.31
129.74
127.47
127.22
127.10
125.21
122.94
121.83
113.53
63.04
56.74
56.54
56.35
OH
CF3
O2N
MeO
2.2n
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-160charac.11.fid
-69.56
OH
CF3
O2N
MeO
2.2n
19F (470 MHz, CDCl3)
f1 (ppm)

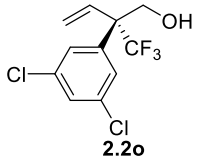


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.449	VV	0.3800	6.37764e4	2676.46704	50.5006
2	12.465	VB	0.3900	6.25120e4	2550.37280	49.4994



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.342	BB	0.3084	1.25027e4	627.64075	96.3681
2	13.393	BB	0.3263	471.19556	21.96116	3.6319

(*S*)-2-(3,5-dichlorophenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2o)



2.2o

Trifluoromethylallene **2.1o** (38.0 mg, 0.15 mmol) was subjected to general procedure G using Ir(cod)(acac), TBAI (10 mol%) and H_2O (500 mol%) in EtOAc at 80 °C. Upon flash column chromatography (SiO_2, 10:90 EtOAc/hexanes), the title compound **2.2o** (24.4 mg, 0.085 mmol) was obtained as a light yellow oil in 57% yield.

R_f = 0.25 (20:80 EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (s, 2H), 7.37 (br s, 1H), 6.07 (dd, *J* = 11.7, 18.7 Hz, 1H), 5.66 (d, *J* = 11.7 Hz, 1H), 5.38 (d, *J* = 18.7 Hz, 1H), 4.22 (dd, *J* = 5.6, 11.1 Hz, 1H), 4.11 (dd, *J* = 5.6, 11.1 Hz, 1H), 1.62 (t, *J* = 5.6 Hz, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 135.1, 132.8, 128.6, 127.9, 126.1 (q, *J* = 285 Hz), 121.7, 63.1, 56.8 (q, *J* = 19.8 Hz).

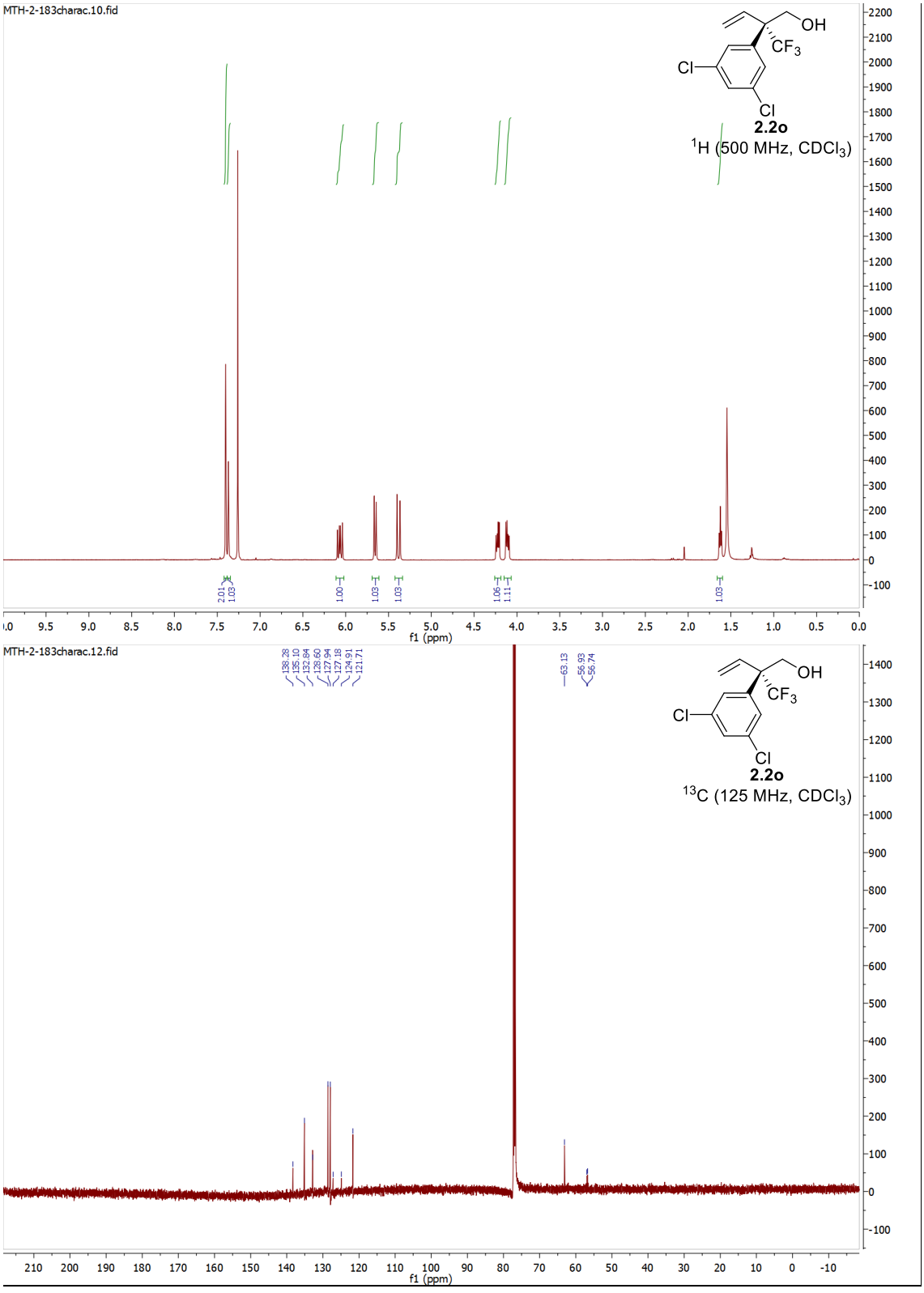
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.8.

HRMS (CI+, *m/z*) for $C_{11}H_9OF_3Cl_2$ = 283.9983; found = 283.9984.

FTIR (neat): 3421, 2939, 1588, 1464, 1421, 1259, 1160, 1071, 942, 859, 802, 689 cm^{-1}.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 90%.

$[\alpha]_D^{27}$ = +31 (c = 1.0, $CHCl_3$).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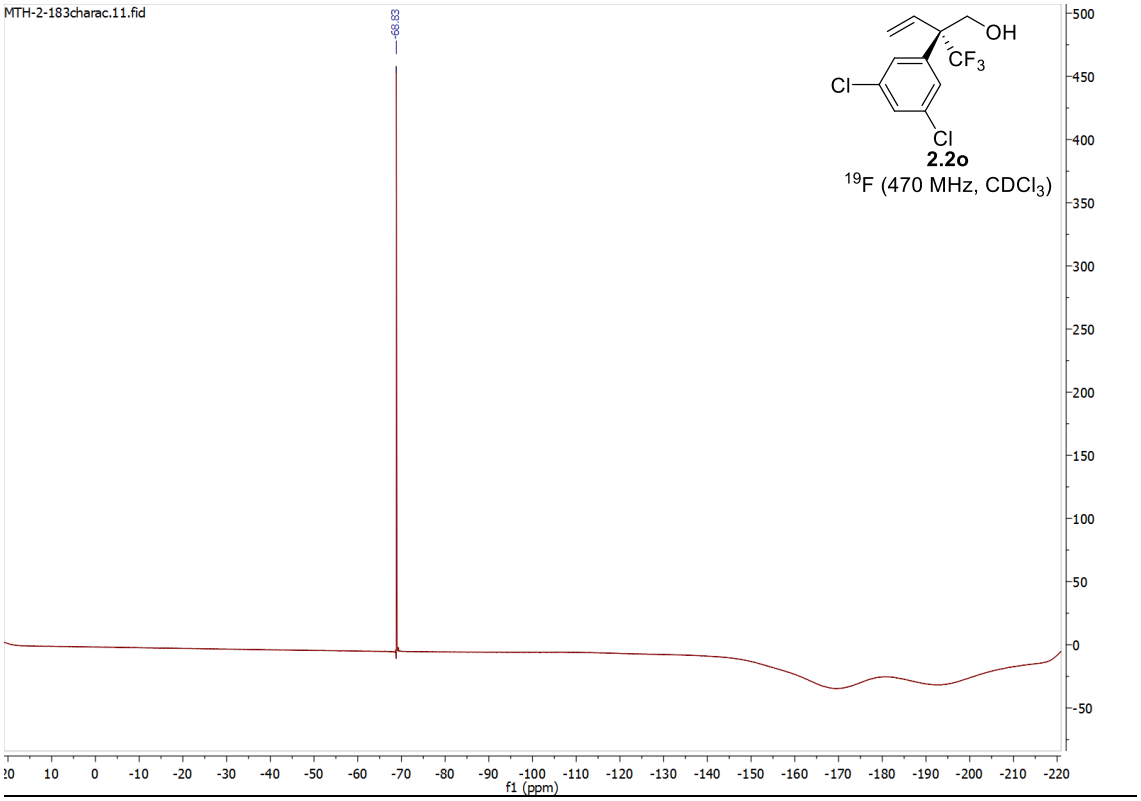
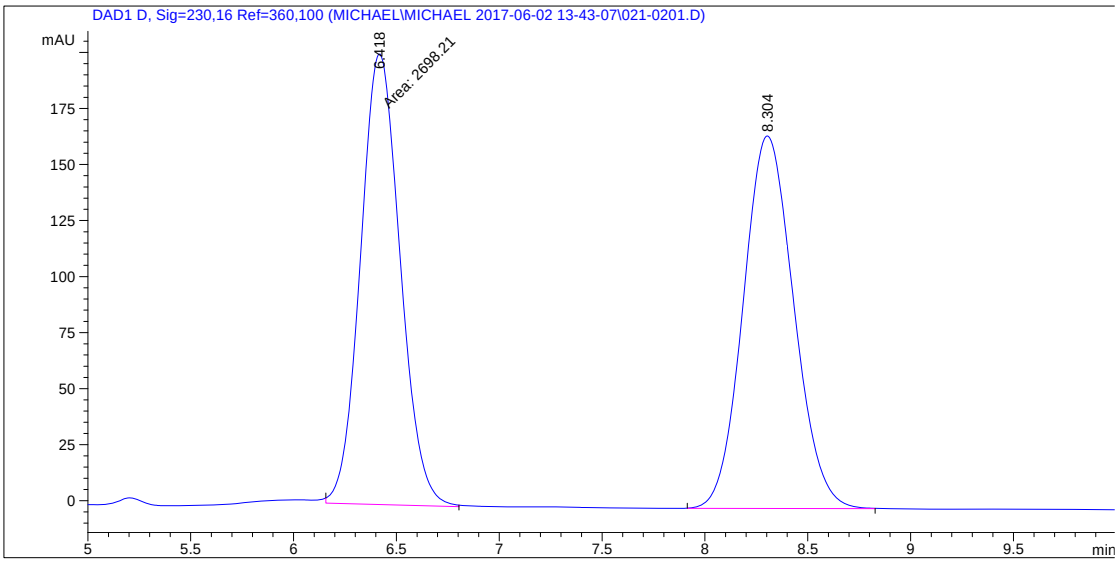
OH
CF3
Cl
Cl
2.2o
1H (500 MHz, CDCl3)
f1 (ppm)
MTH-2-183charac.12.fid
138.28
135.10
132.84
128.60
127.94
127.18
124.91
121.71
63.13
56.93
56.74
OH
CF3
Cl
Cl
2.2o
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-2-183charac.11.fid
-68.83
OH
CF3
Cl
Cl
2.2o
19F (470 MHz, CDCl3)
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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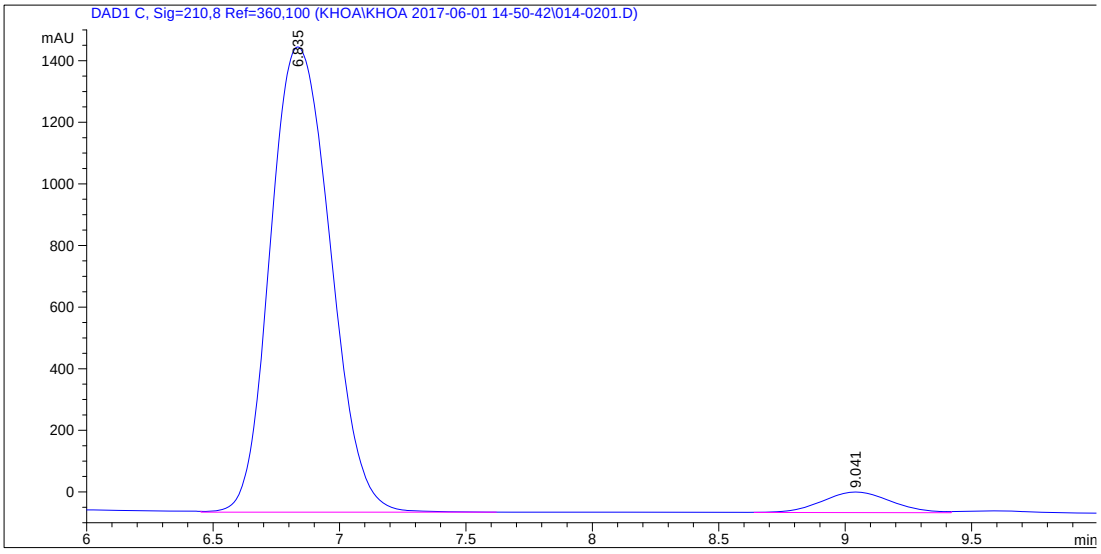
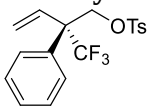
2	8.304	BB	0.2676	2844.11743	166.27774	51.3163



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.835	VB	0.2644	2.49147e4	1510.46399	95.1529
2	9.041	BV	0.2959	1269.16443	66.71927	4.8471

2.5.3.4 Procedures and Spectral Data for the Elaboration of Product 2.2a

(*S*)-2-phenyl-2-(trifluoromethyl)but-3-en-1-yl 4-methylbenzenesulfonate (*pre*-2.3)



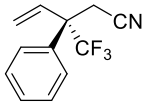
pre-**2.3**

To an oven-dried pressure tube equipped with a magnetic stir bar charged with TsCl (105 mg, 0.55 mmol, 110 mol%) and DMAP (2.0 mg, catalytic) was added alcohol **2.2a** (108.1 mg, 0.5 mmol, 100 mol%) in CH_2Cl_2 (2.5 mL) *via* syringe followed by Et_3N (0.18 mL, 1.25 mmol, 250 mol%). The reaction was allowed to stir at 60 °C for 4 hours. The reaction mixture was allowed to cool to room temperature and CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ (aq, 5 mL) were added. The reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 1:8 EtOAc/hexanes) to furnish the title compound *pre*-**2.3** (168.5 mg, 0.455 mmol) in 91% yield as a colorless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +11.4 (c = 1.14, $CHCl_3$).

The spectral data recorded for this compound was in complete agreement with the literature.[51]

(*S*)-3-phenyl-3-(trifluoromethyl)pent-4-enenitrile (2.3)



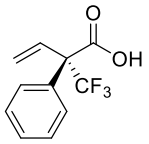
2.3

To an oven-dried pressure tube equipped with a magnetic stir bar charged with *pre*-**2.3** (148 mg, 0.4 mmol, 100 mol%) and sodium cyanide (59.0 mg, 1.2 mmol, 300 mol%) was added DMSO (0.8 mL, 0.5 M). The pressure tube was sealed and the reaction mixture was allowed to stir for 45 hours at 150 °C. The reaction mixture was allowed to cool to room temperature and Et_2O (10 mL) and H_2O (10 mL) were added. The reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 15:85 Et_2O/pentane) to afford title compound **2.3** (56.8 mg, 0.252 mmol) in 63% yield as a colorless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$= -8.85 (c = 1.13, $CHCl_3$).

The spectral data recorded for this compound was in complete agreement with the literature.[51]

(*S*)-2-phenyl-2-(trifluoromethyl)but-3-enoic acid (*pre*-2.4)



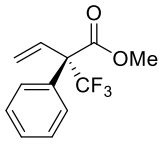
pre-**2.4**

To a flame-dried round bottom flask equipped with magnetic stir bar charged with alcohol **2.2a** (108.1 mg, 0.5 mmol, 100 mol%) was added acetone (5.0 mL, 0.1 M). The reaction mixture was cooled to 0 °C and freshly prepared H_2CrO_4 (0.75 mL, 2.00 M, 300 mol%) was added. The reaction mixture was allowed to stir at room temperature for 5 hours. 2-propanol (5 mL) was slowly added. The reaction mixture was filtered through a pad of cotton and the precipitate was washed with CH_2Cl_2 (10 mL). The filtrate was collected and transferred to a separatory funnel. The organic phase was washed with HCl (1N, 2 × 5 mL), brine (10 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 2:3 EtOAc/hexane) to afford the title compound *pre*-**2.4** (102.4 mg, 0.445 mmol) in 89% yield as a tan solid.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= +38.4 (c = 1.12, $CHCl_3$).

The spectral data recorded for this compound was in complete agreement with the literature.[51]

Methyl (*S*)-2-phenyl-2-(trifluoromethyl)but-3-enoate (2.4)



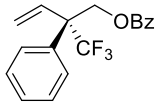
2.4

To an oven-dried pressure tube equipped with magnetic stir bar charged with carboxylic acid *pre*-**2.4** (69.1 mg, 0.3 mmol, 100 mol%) was added methanol (1.2 mL, 0.25 M) and concentrated sulfuric acid (6 μL, 35 mol%). The pressure tube was sealed and the reaction mixture was allowed to stir at 90°C for 16 hours. The reaction mixture was allowed to cool to room temperature and CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 1:8 EtOAc/hexanes) to afford the title compound **2.4** (61.5 mg, 0.252 mmol) in 84% yield as a yellow viscous oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$= +47.5 (c = 1.19, $CHCl_3$).

The spectral data recorded for this compound was in complete agreement with the literature.[51]

(S)-2-phenyl-2-(trifluoromethyl)but-3-en-1-yl benzoate (*pre*-2.5)



pre-**2.5**

To a round bottomed flash equipped with a magnetic stir bar charged with alcohol **2.2a** (108.1 mg, 0.5 mmol, 100 mol%) in CH_2Cl_2 (2.5 mL, 0.2 M) was added benzoyl chloride (80.8 mg, 0.575 mmol, 115 mol%) and Et_3N (105 μL, 0.75 mmol, 150 mol%). The reaction mixture was allowed to stir at room temperature for 10 hours. CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ (aq, 5 mL) were added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 1:10 EtOAc/hexanes) to furnish the title compound *pre*-**2.5** (141 mg, 0.44 mmol) in 88% yield as pale yellow oil.

R_f = 0.65 (4:1 Hexanes: EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H), 7.58 – 7.51 (m, 3H), 7.44 – 7.33 (m, 5H), 6.17 (dd, *J* = 17.8, 11.7 Hz, 1H), 5.59 (d, *J* = 11.7 Hz, 1H), 5.41 (d, *J* = 17.8 Hz, 1H), 4.93 – 4.85 (m, 2H).

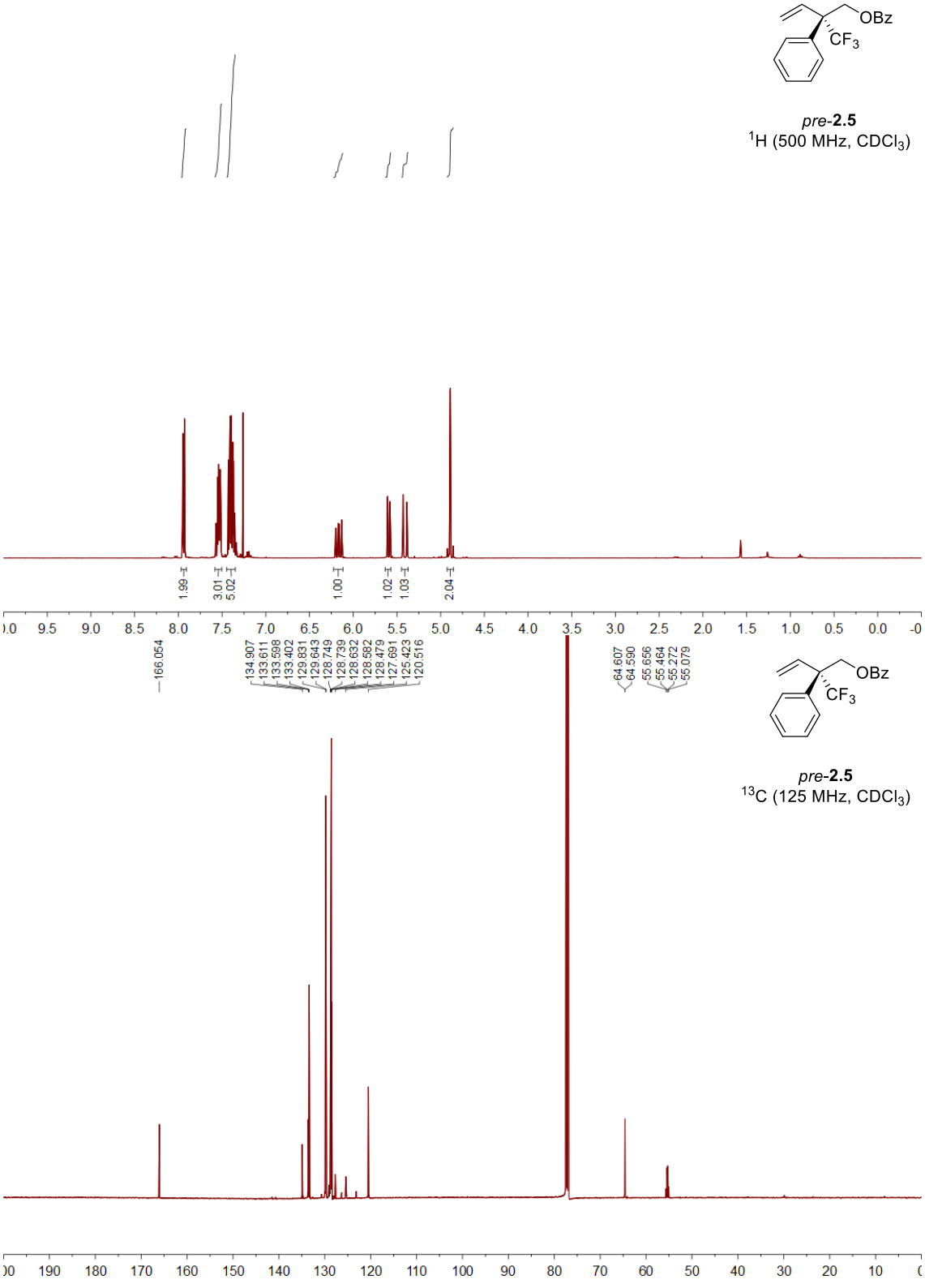
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 134.9, 133.6 (d, *J* = 1.6 Hz), 133.4, 129.8, 129.6, 128.7 (d, *J* = 1.2 Hz), 128.6, 128.6, 128.5, 126.6 (d, *J* = 284.9 Hz), 120.5, 64.6 (d, *J* = 2.2 Hz), 55.4 (q, *J* = 24.2 Hz).

^{19}F NMR (100 MHz, $CDCl_3$): δ -68.6.

HRMS (ESI+, *m/z*) for $C_{18}H_{15}F_3O_2$ $[M+Na]^+$: Calcd. 343.0916, Found 343.0920.

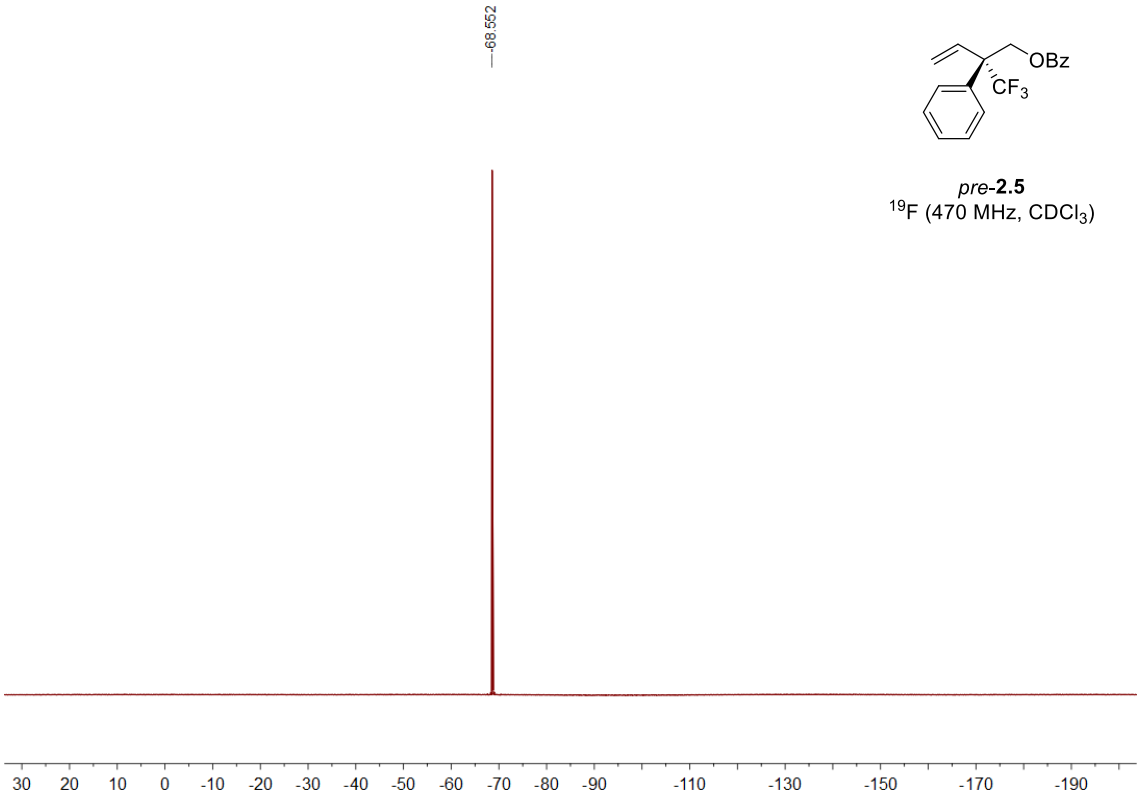
FTIR (neat): 3063, 2366, 1775, 1723, 1601, 1450, 1269, 1151, 936, 871, 699 cm^{-1}.

$[\alpha]_D^{24}$ = +59.4 (c = 1.14, $CHCl_3$).



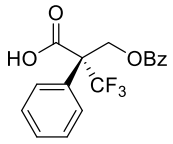
pre-**2.5**
^{1}H (500 MHz, $CDCl_3$)

pre-**2.5**
^{13}C (125 MHz, $CDCl_3$)



pre-**2.5**
^{19}F (470 MHz, $CDCl_3$)

(*S*)-2-((Benzoyloxy)methyl)-3,3,3-trifluoro-2-phenylpropanoic acid (2.5)



2.5

To a round bottom flask equipped with a magnetic stir bar charged with $NaIO_4$ (3.2 mmol, 0.684 g, 800 mol%) in pH 7.0 buffer (20 mL, 0.02 M) was added $KMnO_4$ (0.4 mmol, 63.2 mg, 100 mol%) and the reaction mixture was allowed to stir for 15 minutes at room temperature. *Pre*-**2.5** (0.4 mmol, 128.1 mg, 100 mol%) in *t*-BuOH (20 mL, 0.02M) was added *via* syringe and the reaction mixture was allowed to stir at room temperature for 15 hours. $Na_2S_2O_3.5H_2O$ (300 mol%, 1.2 mmol, 298 mg) was added and the reaction mixture was allowed to stir for 45 minutes. H_2O (20 mL) and EtOAc (20 mL) were added and the reaction mixture was allowed to stir for a further 30 minutes. The reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were washed with HCl (1N, 3 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 1:19 MeOH/CH_2Cl) to furnish the title compound **2.5** (83.9 mg, 0.248 mmol) in 62% yield as a white solid.

R_f = 0.25 (CH_2Cl_2/MeOH = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 – 7.95 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 – 7.34 (m, 7H), 6.46 (bs, 1H), 5.13 (d, *J* = 11.3 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 165.7, 133.6, 131.2, 129.9, 129.6, 129.3, 129.2, 128.8, 128.7, 127.7, 64.4, 60.4 (q, *J* = 25.8 Hz)

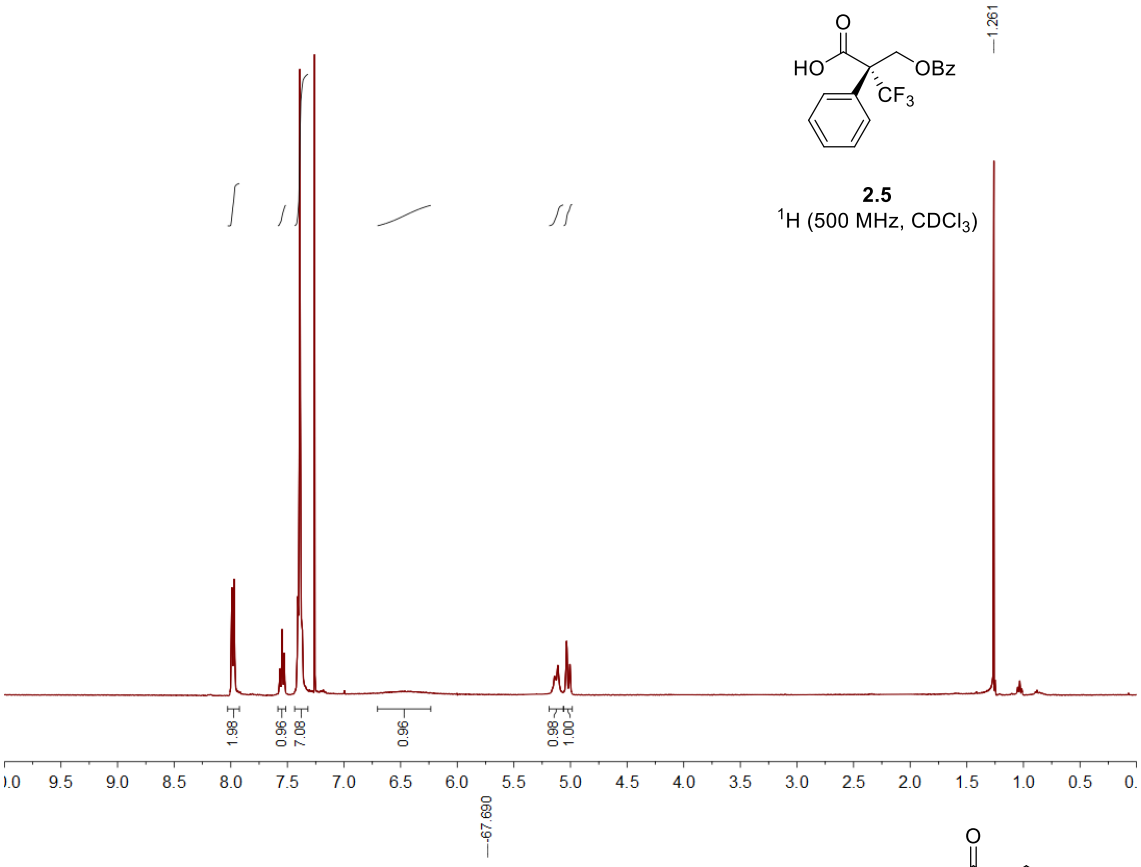
^{19}F NMR (100 MHz, $CDCl_3$) δ: -67.7.

HRMS: Compound decomposed in GC due to decarboxylation/elimination of benzoic acid. Compound 10 was observed plus benzoic acid

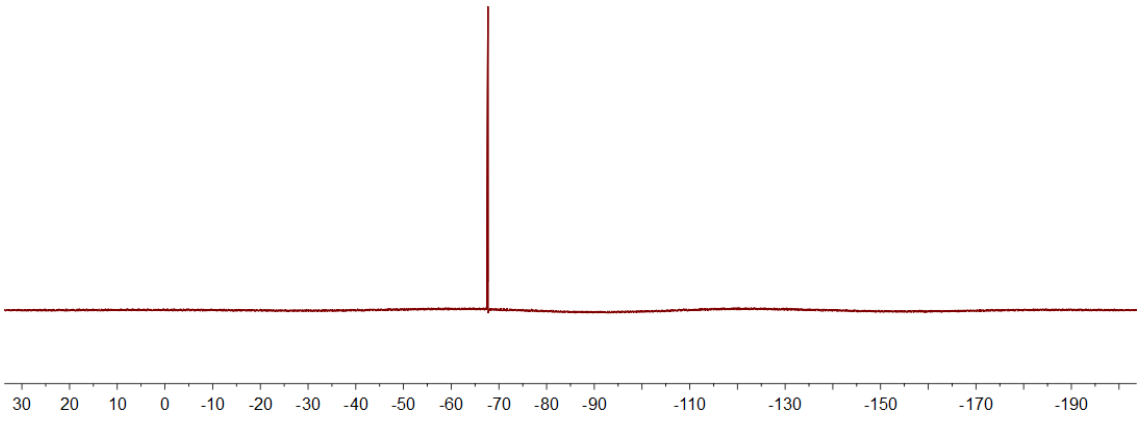
MP: 131.8 – 132.6 ^{o}C

FTIR (neat): 3139 (b), 2978, 2360, 1754, 1725, 1692, 1601, 1453, 1289, 1173, 1069, 942, 698 cm^{-1}.

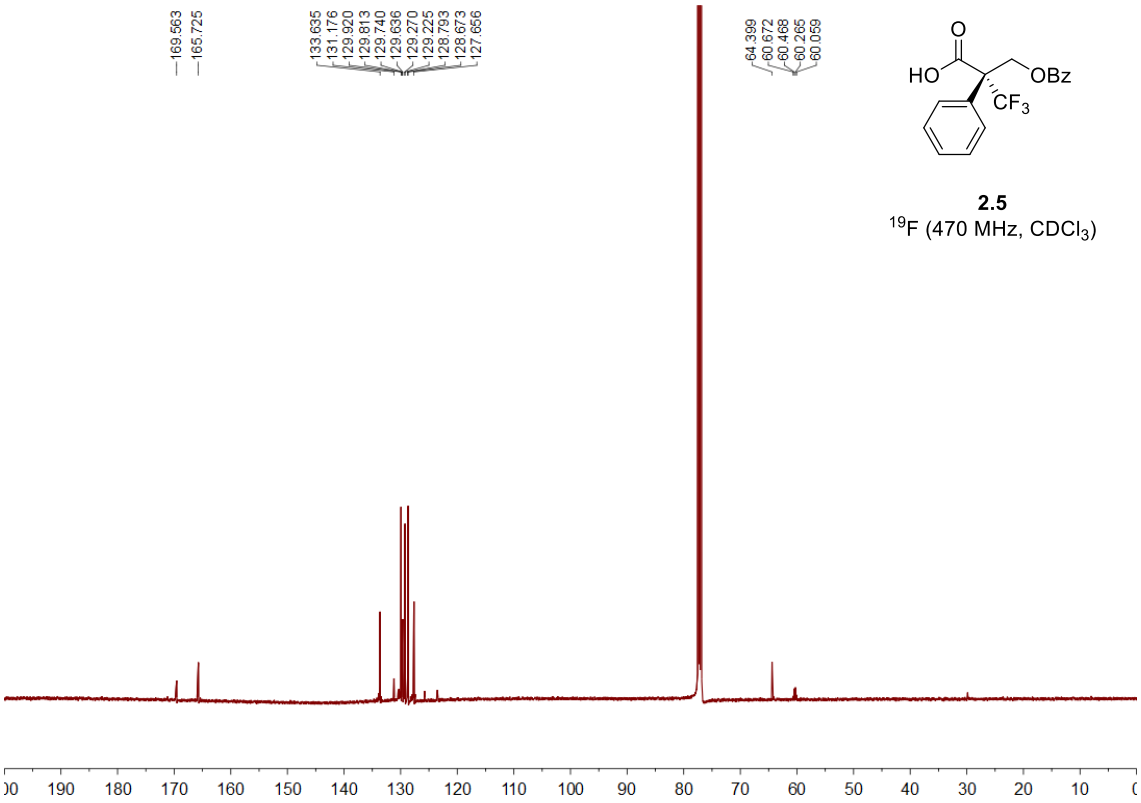
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= -34.1 (c = 1.13, $CHCl_3$).



2.5
^{1}H (500 MHz, $CDCl_3$)



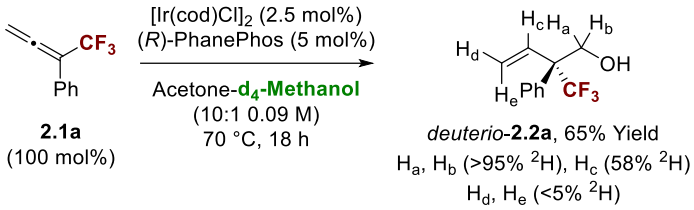
2.5
^{13}C (125 MHz, $CDCl_3$)



2.5

^{19}F (470 MHz, $CDCl_3$)

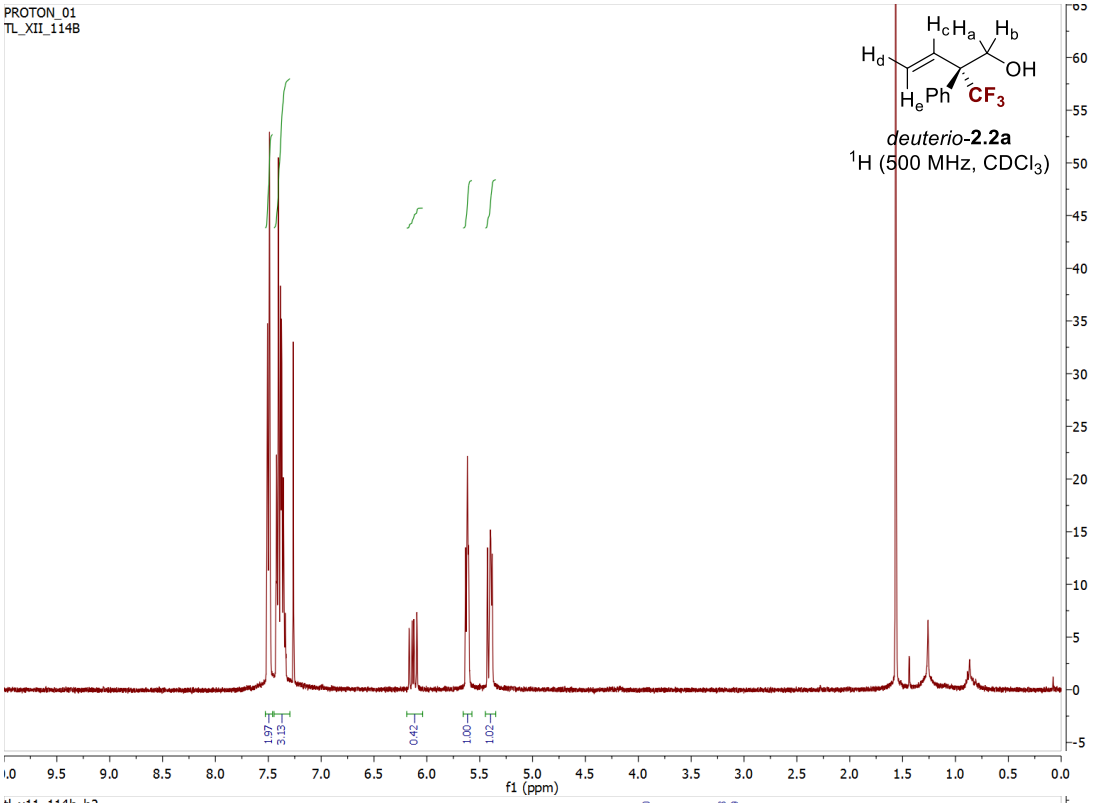
2.5.3.5 Isotopic Labeling Studies

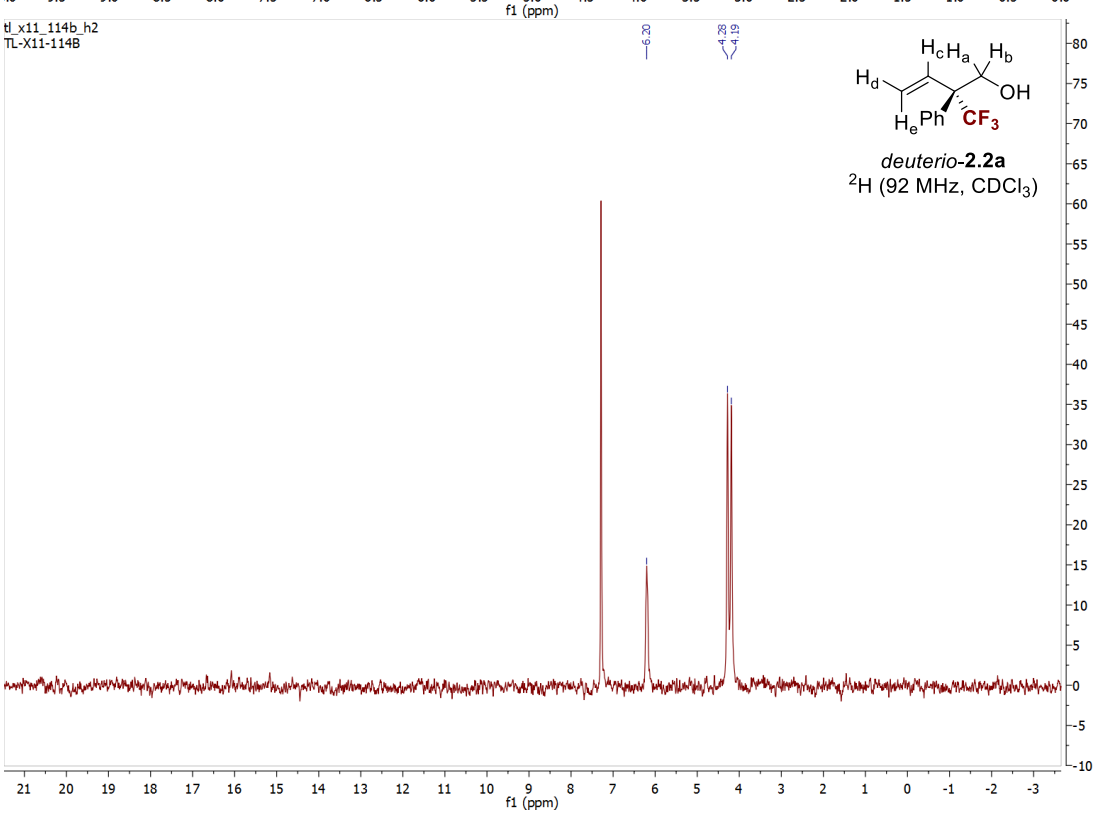


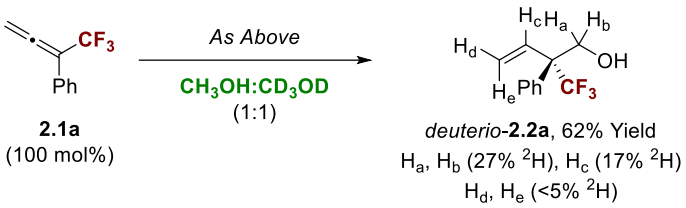
Trifluoromethylallene **2.1a** (33.0 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C with d_4-MeOH instead of MeOH.

HRMS (CI+, m/z) for C11H9D2OF3 = 218.0888; found = 218.0893;

HRMS (CI+, m/z) for C11H8D3OF3 = 219.0950; found = 219.0953.


PROTON_01
TL_XII_114B
H_cH_a H_b
H_d
OH
H_ePh CF_3
deuterio-**2.2a**
^{1}H (500 MHz, $CDCl_3$)
1.97
3.13
0.42
1.00
1.02
f1 (ppm)

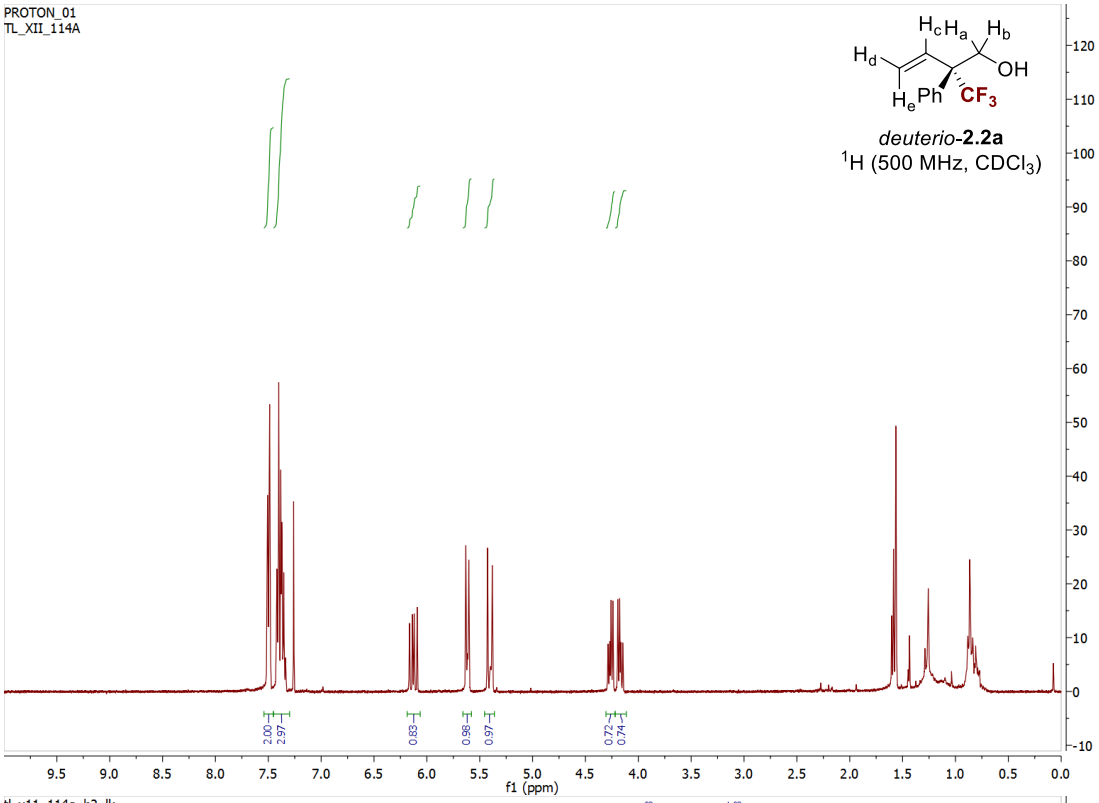

tl_x11_114b_h2
TL-X11-114B
6.20
4.28
4.19
H_cH_a H_b
H_d
OH
H_ePh CF_3
deuterio-**2.2a**
^{2}H (92 MHz, $CDCl_3$)
f1 (ppm)

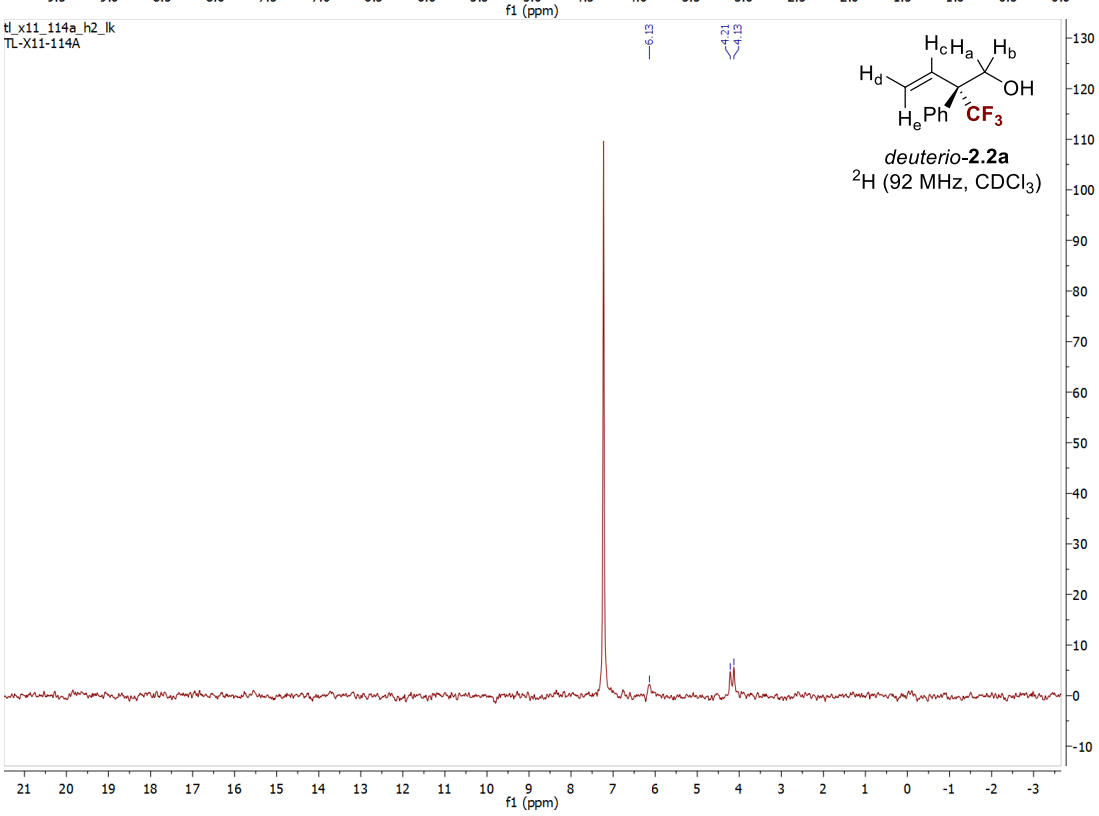


Trifluoromethylallene **2.1a** (33.0 mg, 0.15 mmol) was subjected to general procedure G using $[Ir(cod)Cl]_2$ in Me_2CO at 70 °C with 1:1 d_4-MeOH:MeOH added.

HRMS (CI+, *m/z*) for $C_{11}H_9D_2OF_3$ = 218.0888; found = 218.0891;

HRMS (CI+, *m/z*) for $C_{11}H_8D_3OF_3$ = 219.0950; found = 219.0952.


PROTON_01
TL_XII_114A
H_cH_a H_b
H_d
OH
H_ePh CF_3
deuterio-**2.2a**
^{1}H (500 MHz, $CDCl_3$)
2.00
2.97
0.83
0.98
0.97
0.72
0.74
f1 (ppm)

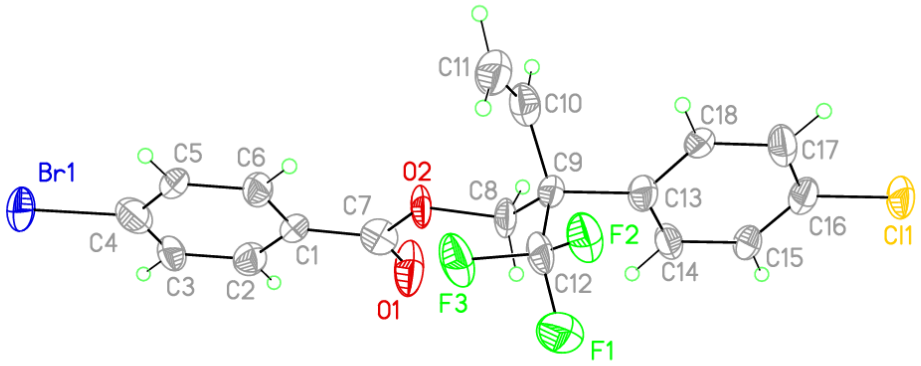

tl_x11_114a_h2_lk
TL-X11-114A
6.13
4.21
4.13
H_cH_a H_b
H_d
OH
H_ePh CF_3
deuterio-**2.2a**
^{2}H (92 MHz, $CDCl_3$)
f1 (ppm)

2.5.3.6 Crystallographic Material for Coupling Product 2.2b and 2.2f (4-Bromobenzoate Derivative)

Single Crystal Diffraction Data for Coupling Product 3.2b

Empirical formula	C18 H13 Br Cl F3 O2	
Formula weight	433.64	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.375(10) Å	σ= 90°.
	b = 7.357(6) Å	β= 116.91(4)°.
	c = 11.576(9) Å	γ = 90°.
Volume	863.8(13) $Å^3$	
Z	2	
Density (calculated)	1.667 Mg/m^3	
Absorption coefficient	2.573 mm^{-1}	
F(000)	432	
Crystal size	0.260 x 0.097 x 0.054 mm^3	
Theta range for data collection	1.973 to 25.558°.	
Index ranges	-13<=h<=13, -8<=k<=8, -13<=l<=13	
Reflections collected	8167	
Independent reflections	3054 [R(int) = 0.1043]	
Completeness to theta = 25.242°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.739	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3054 / 151 / 226	
Goodness-of-fit on F^2	0.945	
Final R indices [I>2sigma(I)]	R1 = 0.0597, wR2 = 0.1302	
R indices (all data)	R1 = 0.1159, wR2 = 0.1512	
Absolute structure parameter	0.025(15)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.973 and -0.742 $e.Å^{-3}$	

Figure 2.7 Crystal Structure of **2.2b** 4-Bromobenzoate Derivative

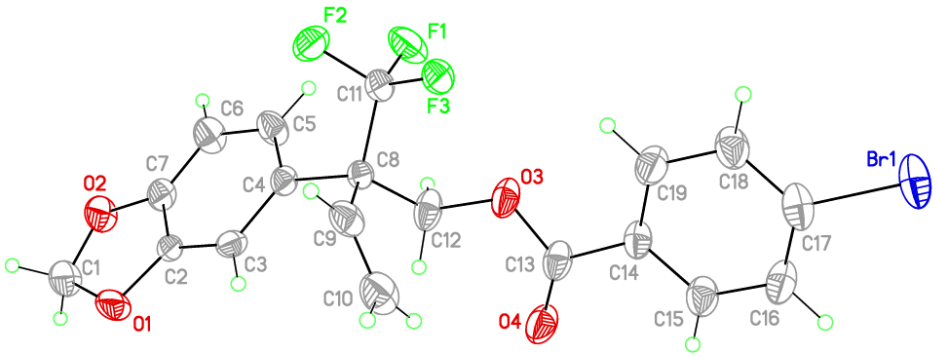


View of **2.2b** 4-Bromobenzoate derivative showing the atom labelling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Single Crystal Diffraction Data for Coupling Product 2.2f 4-Bromobenzoate

Empirical formula	C19 H14 Br F3 O4	
Formula weight	443.21	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P 1	
Unit cell dimensions	a = 6.7013(13) Å	α= 76.249(5)°.
	b = 9.3224(18) Å	β= 85.028(5)°.
	c = 14.718(3) Å	γ = 81.015(5)°.
Volume	881.0(3) $Å^3$	
Z	2	
Density (calculated)	1.671 Mg/m^3	
Absorption coefficient	2.386 mm^{-1}	
F(000)	444	
Crystal size	0.210 x 0.200 x 0.160 mm^3	
Theta range for data collection	3.082 to 27.476°.	
Index ranges	-8<=h<=8, -12<=k<=12, -19<=l<=18	
Reflections collected	13880	
Independent reflections	7401 [R(int) = 0.0301]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.779	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7401 / 436 / 643	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0808	
R indices (all data)	R1 = 0.0387, wR2 = 0.0838	
Absolute structure parameter	0.014(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.529 and -0.258 $e.Å^{-3}$	

Figure 2.8 Crystal Structure of **2.2f** 4-Bromobenzoate Derivative

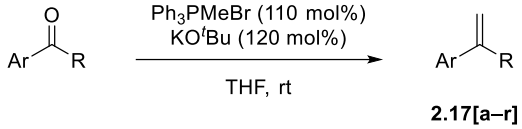


View of **2.2f** 4-bromobenzoate derivative showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

2.5.4 Experimental Data for Section 2.3

2.5.4.1 General Procedures

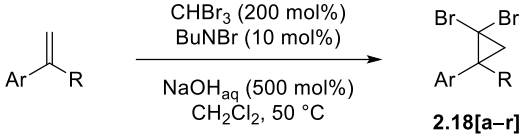
General Procedure H



2.17[a–r]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with methyltriphenylphosphonium bromide (110 mol%) in THF (0.25M) at 0 °C was added potassium *tert*-butoxide (120 mol%). The reaction mixture was allowed to stir at room temperature for 1 hour. Acetophenone (100 mol%) was added and the reaction mixture was allowed to stir at room temperature for 16 hours. To the reaction mixture was added H_2O. The reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the styrenes.

General Procedure I

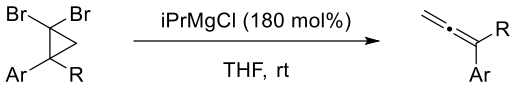


2.18[a–r]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with styrene (100 mol%), bromoform (200 mol%) and tetrabutylammonium bromide (10 mol %) in CH_2Cl_2 (3M) was added dropwise sodium hydroxide (50% in H_2O, 500 mol%). The reaction mixture was allowed to stir for 24 hours at 50 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc, and H_2O was added. The reaction mixture was transferred to a separatory funnel and the aqueous layer was extracted

with EtOAc (3x). The combined organic extracts were washed with aqueous HCl (1N), H_2O and brine. The solution was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the 1,1-dibromo-cyclopropanes.

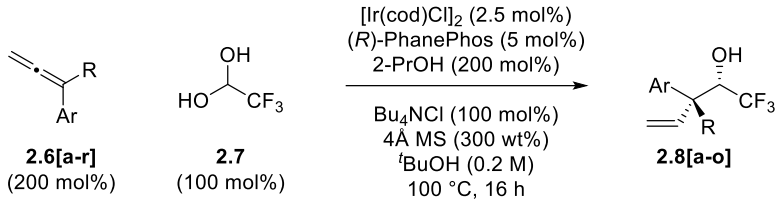
General Procedure J



2.6[a–r]

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with cyclopropane (100 mol%) in THF (0.5 M) was added dropwise isopropylmagnesium chloride (2M in THF, 180 mol%). The reaction mixture was allowed to stir for 1 hour at room temperature. Aqueous HCl (1N) was added to the reaction mixture and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3x) and the combined organic extracts were washed with brine. The solution was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the 1,1-disubstituted allenes.

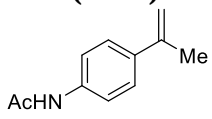
General Procedure K



To a dried pressure tube under an argon atmosphere charged with $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-PhanePhos (5 mol%), tetrabutylammonium chloride (100 mol%) and dried 4 Å molecular sieves (300 wt%) was added 1,1-disubstituted allene (200 mol%), isopropanol (200 mol%) and tert-butanol (0.2M) followed by fluoral hydrate (100 mol%). The reaction mixture was allowed to stir for 16 hours at 100 °C. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (SiO_2) under the noted conditions to furnish the fluoral adducts.

2.5.4.2 Procedures and Spectral Data for 1,1-Disubstituted Allenes 2.6[a–u]

_N_-(4-(prop-1-en-2-yl)phenyl)acetamide (2.17f)

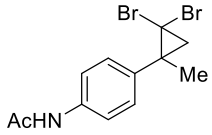


2.17f

4’-acetamidoacetophenone (2.51 g, 14.20 mmol) was subjected to general procedure H. Upon flash column chromatography (SiO_2, 1:2 EtOAc/hexanes), the title compound **2.17f** (1.99 g, 11.35 mmol) was obtained as a light yellow solid in 80% yield

The spectral data recorded for this compound was in complete agreement with the literature.[55]

***N*-(4-(2,2-dibromo-1-methylcyclopropyl)phenyl)acetamide (2.18f)**



2.18f

Styrene **2.17f** (1.99 g, 11.35 mmol) was subjected to general procedure I. Upon flash column chromatography (SiO_2, 1:1 EtOAc/hexanes), the title compound **2.18f** (2.33 g, 6.72 mmol) was obtained as a clear oil in 59% yield.

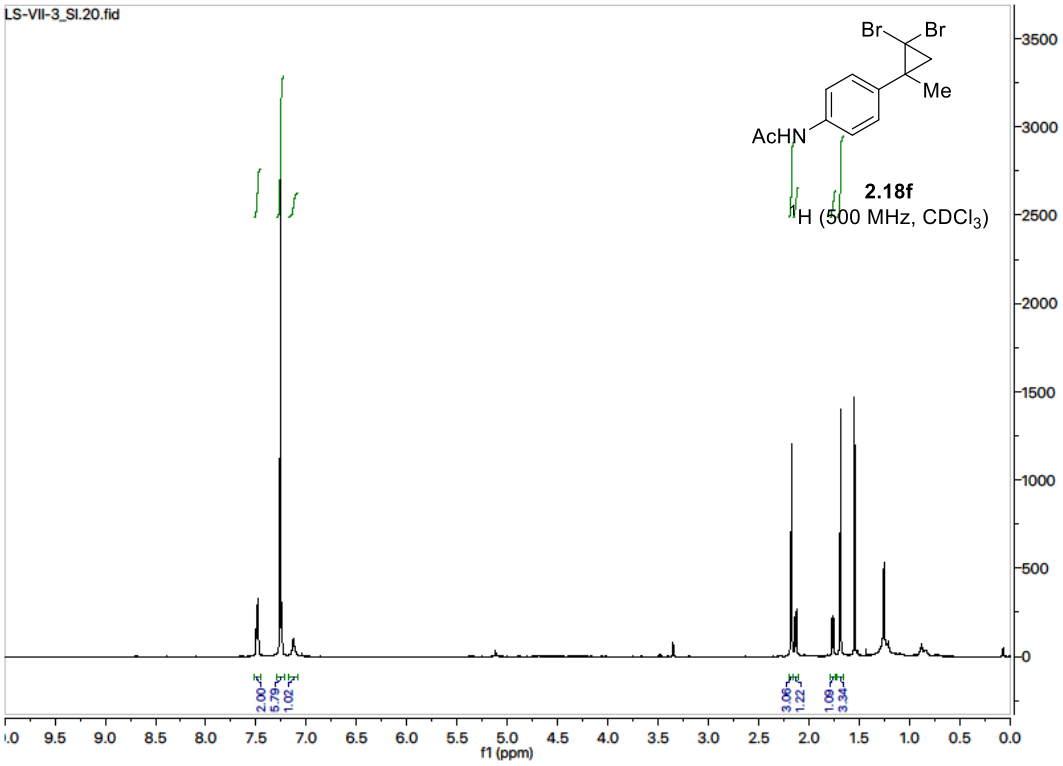
R_f = 0.3 (10:1 CH_2Cl_2 : MeOH)

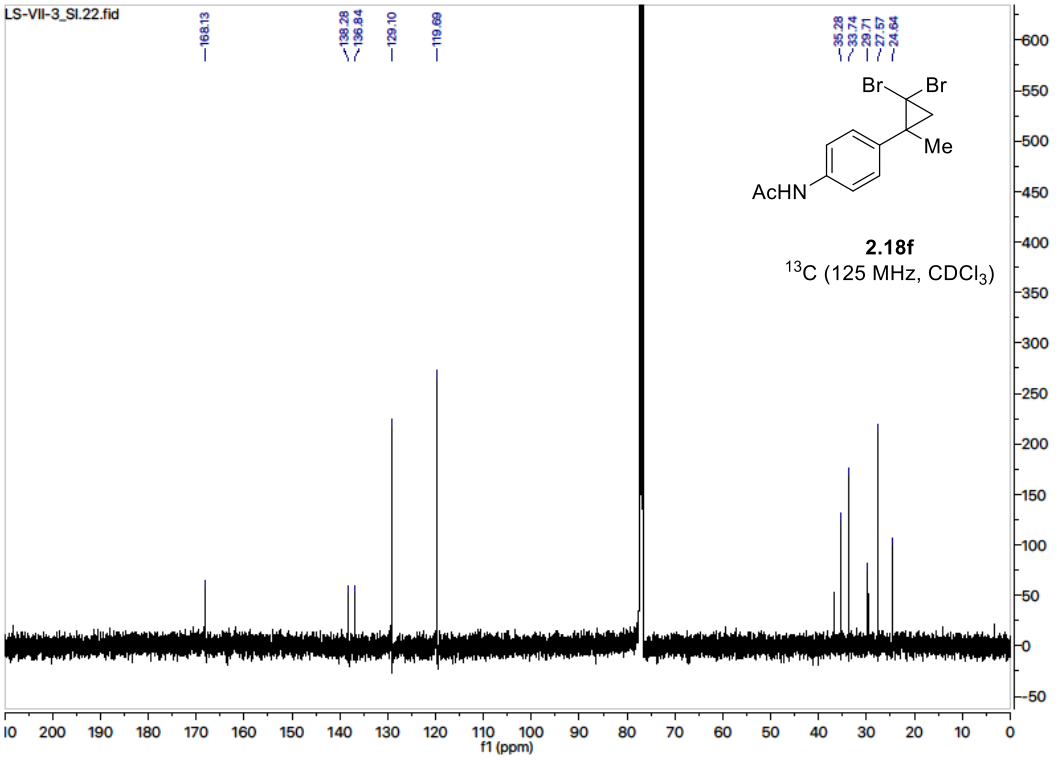
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.13 (bs, 1H), 2.18 (s, 3H), 2.13 (d, *J* = 7.4 Hz, 1H), 1.76, (d, *J* = 7.6 Hz, 1H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1, 138.3, 136.8, 129.1, 119.7, 35.3, 33.7, 29.7, 27.6, 24.6.

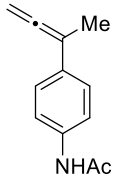
HRMS (ESI+H, *m/z*) for $C_{12}H_{13}Br_2NO$: calcd. = 345.9437; found = 345.9434.

FTIR (neat): 3300, 2900, 2400, 1700, 1600, 1500, 1350, 800 cm^{-1}.


LS-VII-3_SI.20.fid
Br
Br
Me
AcHN
2.18f
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


LS-VII-3_SI.22.fid
168.13
138.28
136.84
129.10
119.69
35.28
33.74
29.71
27.57
24.64
Br
Br
Me
AcHN
2.18f
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

***N*-(4-(buta-2,3-dien-2-yl)phenyl)acetamide (2.6f)**



2.6f

1,1-disubstituted cyclopropane **2.18f** (2.33 g, 6.72 mmol) was subjected to general procedure J. Upon flash column chromatography (SiO_2, 1:2 EtOAc:hexanes), the title compound **2.6f** (968.8 mg, 5.17 mmol) was obtained as a light yellow solid in 79% yield.

R_f = 0.3 (1:1 hexanes : EtOAc)

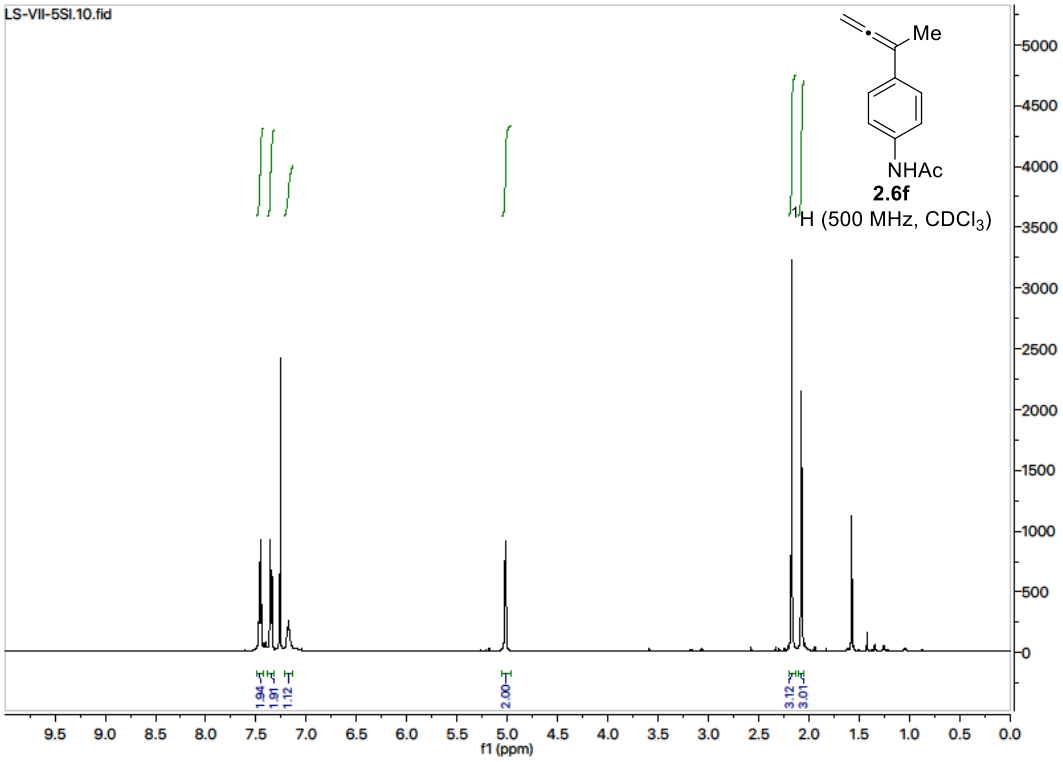
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.18 (bs, 1H), 5.02 (q, *J* = 3.1 Hz, 2H), 2.17 (s, 3H), 2.07 (t, *J* = 3.1 Hz, 3H).

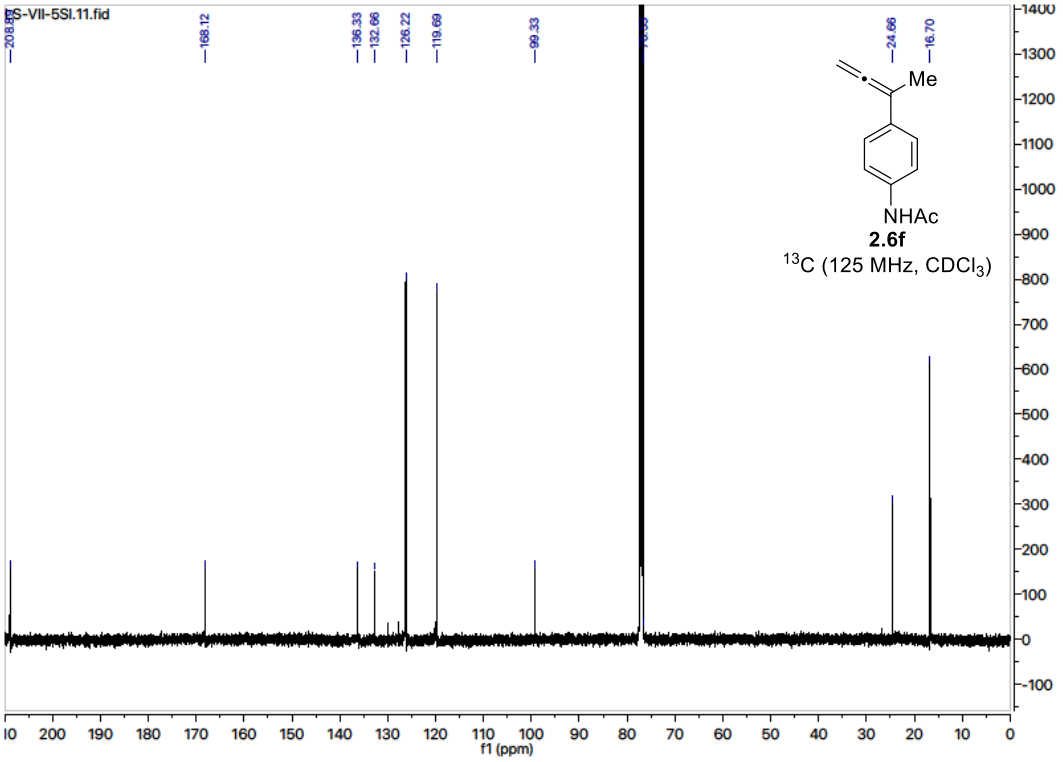
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.9, 168.1, 136.3, 132.7, 126.2, 119.7, 99.3, 76.6, 24.7, 16.7.

HRMS (ESI+H, *m/z*) for $C_{12}H_{13}NO$: calcd. = 188.1070; found = 188.1073.

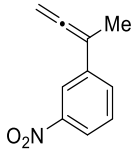
FTIR (neat): 3300, 3000, 2350, 1650, 1600, 1550, 1500, 1400, 1350, 1300, 800 cm^{-1}.

MP: 66-68 °C


LS-VII-5SI.10.fid
Me
NHAc
2.6f
^{1}H (500 MHz, $CDCl_3$)
1.94
1.91
1.12
2.00
3.12
3.01
f1 (ppm)


LS-VII-5SI.11.fid
168.12
136.33
132.66
126.22
119.69
99.33
24.66
16.70
Me
NHAc
2.6f
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

1-(buta-2,3-dien-2-yl)-3-nitrobenzene (2.6j)

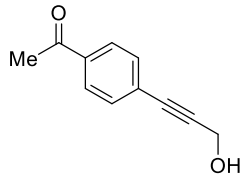


2.6j

In a dry rounded bottom flask with indium (0.92 g, 8 mmol), was added anhydrous DMF (8 mL) and 1-bromo-2-butyne (1.05 mL, 12 mmol, 150 mol %) under nitrogen atmosphere. After 1 hour, the resulting homogenous solution was added to a suspension of 3-nitroiodobenzene (2.00 g, 8.00 mmol, 100 mol %), $Pd(PPh_3)_4$ (0.37 g, 0.32 mmol, 4 mol %) and lithium iodide (3.21 g, 24 mmol, 300 mol %) in anhydrous DMF (8 mL). This mixture was stirred at 100 ^oC for 1 h, cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic solvents were washed with water (20 m L) and brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexanes/EtOAc 20:1 to give the desired allene **2.6j** (0.49 g, 2.80 mmol) as a yellow oil in 35 % yield.[56]

The spectral data recorded for this compound was in complete agreement with the literature.[57]

1-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)ethan-1-one (2.19k)

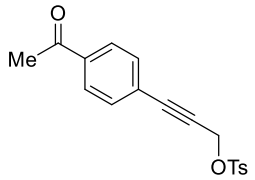


2.19k

In a dry pressure tube with 4-bromoacetophenone (2.0 g, 10 mmol), $PdCl_2(PPh_3)_2$ (0.14 g, 0.2 mmol, 2 mol %), copper (I) iodide (0.19 g, 1 mmol, 10 mol %) was purged with argon and propargyl alcohol (0.71 mL, 12 mmol, 120 mol %) and triethylamine (20 mL) were added. The resulting mixture was heated to 80 ^oC for 12 h, cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL), and the combined organic solvents were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane/EtOAc 3:1 to give the desired alcohol (1.74 g, 10 mmol) as white solid in 99 % yield.

The spectral data recorded for this compound was in complete agreement with the literature.[58]

3-(4-acetylphenyl)prop-2-yn-1-yl 4-methylbenzenesulfonate (2.20k)

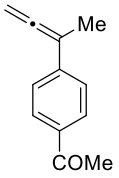


2.20k

In a dry rounded bottom flask with 1-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)ethan-1-one **2.19k** (1.0 g, 5.74 mmol) and tosyl chloride (1.20 g, 6.31 mmol, 110 mol %), was added diethyl ether (8 mL) and then potassium hydroxide (1.61 g, 28.7 mmol, 500 mol %) at 0 ^{o}C. The mixture was allowed to warm to room temperature and after 1 h was quenched with water (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic solvents were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane/EtOAc 2:1 to give the desired tosylate **2.20k**(1.40 g, 4.26 mmol) as white solid in 74 % yield.

The spectral data recorded for this compound was in complete agreement with the literature.[59]

1-(4-(buta-2,3-dien-2-yl)phenyl)ethan-1-one (2.6k)



2.6k

In a dry rounded bottom flask with cupper (I) bromide (0.48 g, 3.33 mmol, 100 mol %) purged with nitrogen atmosphere in THF (10 mL) was added methylmagnesium bromide (1.1 mL, 100 mol %, 3 M) dropwise. After 1 h, a THF (10 mL) solution of 3-(4-acetylphenyl)prop-2-yn-1-yl 4-methylbenzenesulfonate **2.20k** (1.04 g, 3.17 mmol) was added dropwise and the solution was allowed to stir at room temperature for 1 h. After 1 h, reaction was quenched with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic solvents were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane/EtOAc 10:1 to give the desired allene **2.6k** (0.21 g, 1.21 mmol) as clear oil in 38 % yield.

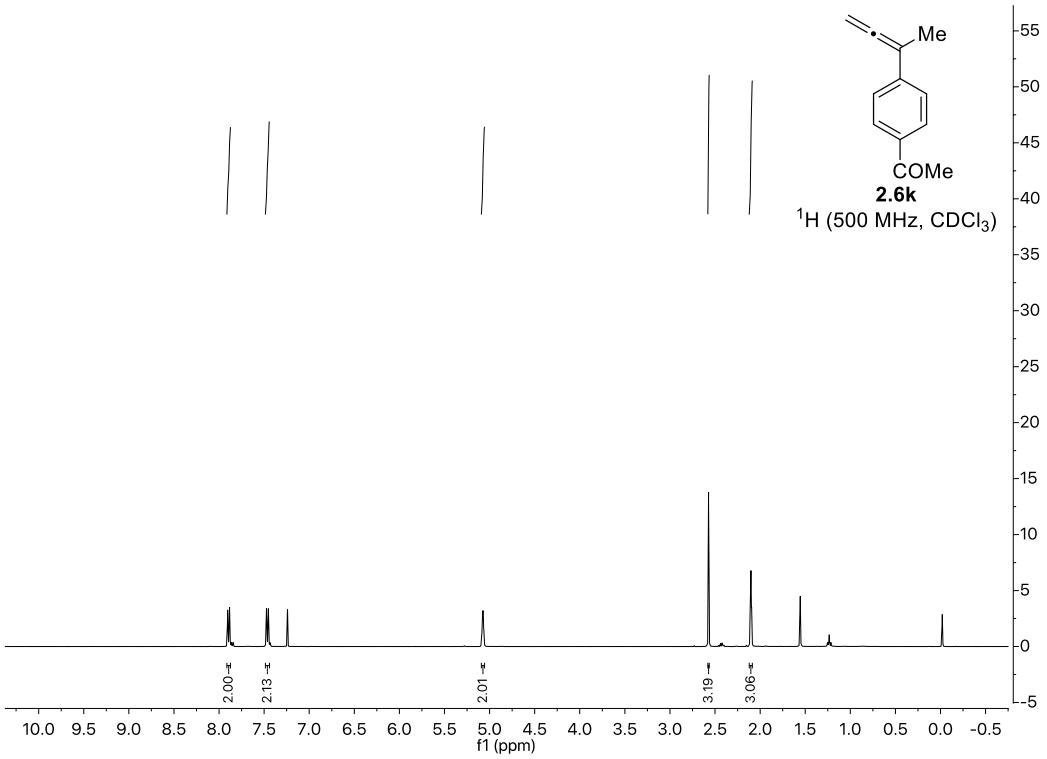
R_f = 0.51 (5:1 hexanes : EtOAc)

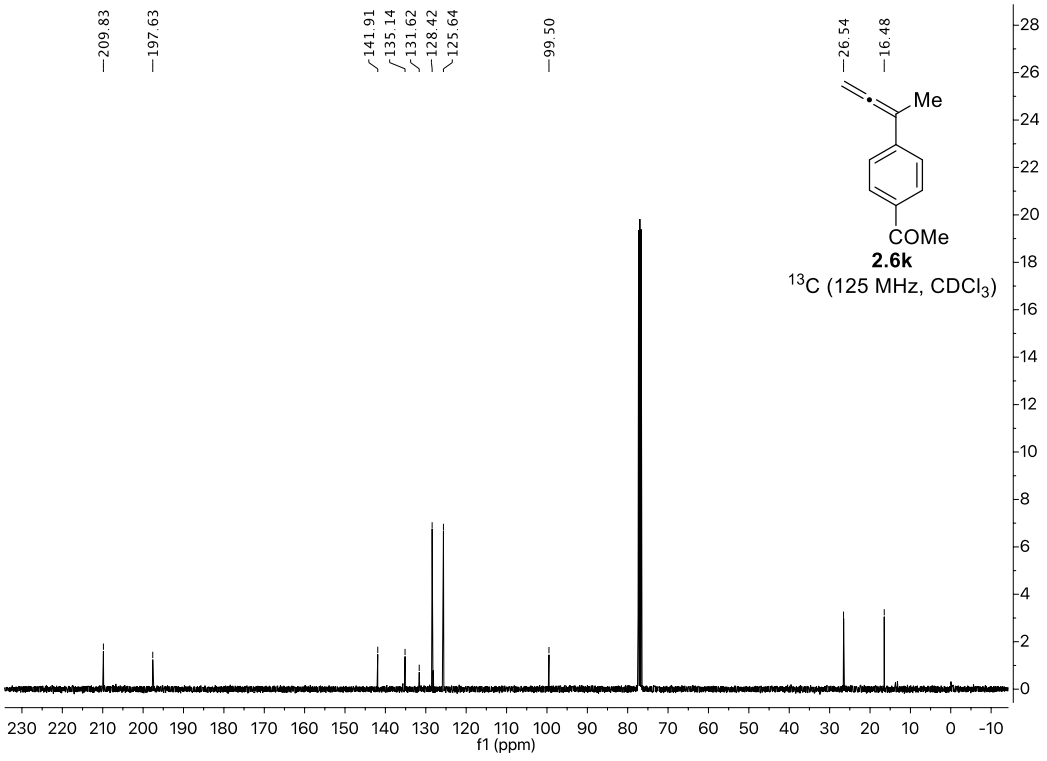
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 5.07 (q, *J* = 3.2 Hz, 2H), 2.57 (s, 3H), 2.12 – 2.09 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.8, 197.6, 141.9, 135.1, 131.6, 128.4, 125.6, 99.5, 26.5, 16.5.

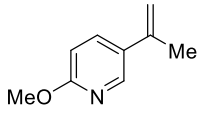
HRMS (ESI + H, *m/z*) for $C_{12}H_{13}O$: calcd. = 173.0963; found = 173.0961.

FTIR (neat): 2944, 2866, 1682, 1462, 1356, 1192, 996, 976, 882, 826, 678, 662 cm^{-1}.


Me
COMe
2.6k
1H (500 MHz, CDCl3)
2.00
2.13
2.01
3.19
3.06
f1 (ppm)


209.83
197.63
141.91
135.14
131.62
128.42
125.64
99.50
26.54
16.48
Me
COMe
2.6k
13C (125 MHz, CDCl3)
f1 (ppm)

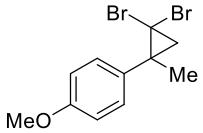
2-Methoxy-5-(prop-1-en-2-yl)pyridine (2.17m)



2.17m

5-Acetyl-2-methoxypyridine (1.51 g, 10 mmol) was subjected to general procedure H. The product was passed through a short silica plug (EtOAc) and used in the next step without further purification.

5-(2,2-Dibromo-1-methylcyclopropyl)-2-methoxypyridine (2.18m)



2.18m

Styrene **2.17m** (10 mmol) was subjected to general procedure I. Upon flash column chromatography (SiO_2, 3:97 EtOAc:hexanes), the title compound **2.18m** (1.63 g, 5.5 mmol) was obtained as a light yellow solid in 55% yield over two steps.

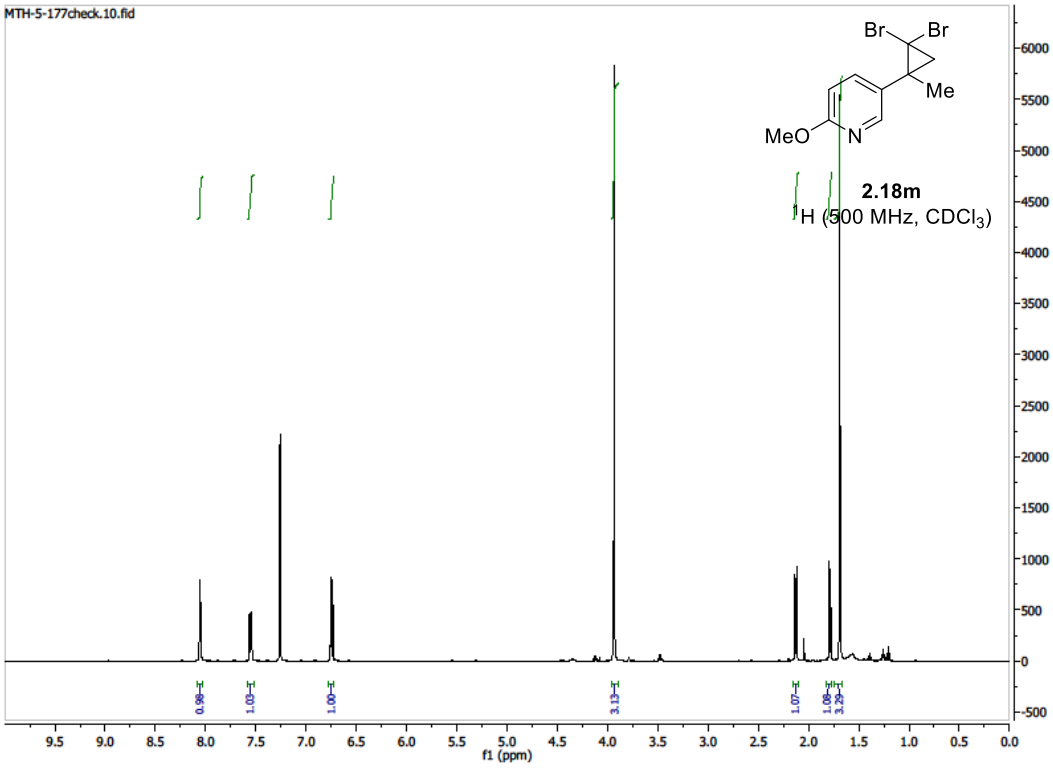
R_f = 0.32 (95:5 hexanes:EtOAc)

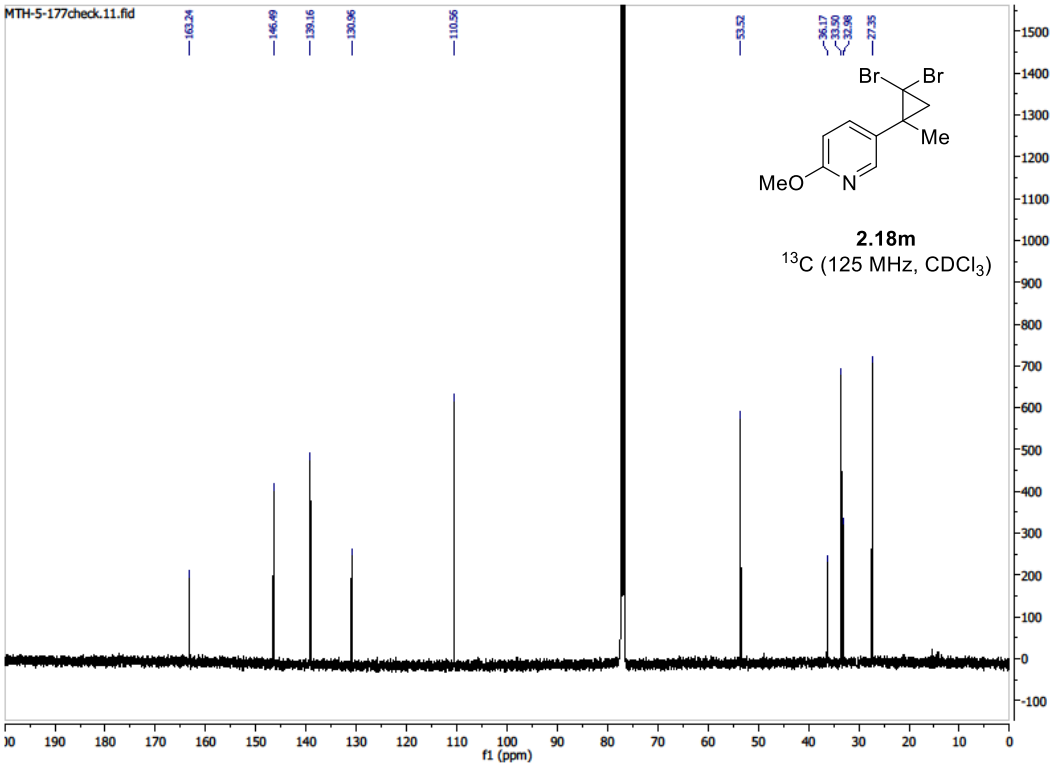
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 2.5 Hz, 1H), 7.55 (dd, *J* = 2.5, 8.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 3H), 2.13 (d, *J* = 7.3 Hz, 1H), 1.79 (d, *J* = 7.3 Hz, 1H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.2, 146.5, 139.2, 131.0, 110.6, 53.5, 36.2, 33.5, 33.0, 27.4.

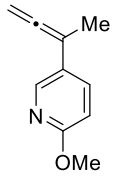
HRMS (ESI+H, *m/z*) for $C_{10}H_{11}Br_2NO$: calcd. = 319.9280; found = 319.9277.

FTIR (neat): 2982, 1608, 1495, 1375, 1309, 1063, 1023, 832 cm^{-1}.


MTH-5-177check.10.fid
Br
Br
Me
MeO
N
2.18m
H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-177check.11.fid
163.24
146.49
139.16
130.96
110.56
53.52
36.17
33.50
32.98
27.35
Br
Br
Me
MeO
N
2.18m
13C (125 MHz, CDCl3)
f1 (ppm)

5-(Buta-2,3-dien-2-yl)-2-methoxypyridine (2.6m)



2.6m

1,1-Disubstituted cyclopropane **2.18m** (1.63 g, 5.5 mmol) was subjected to general procedure J. Upon flash column chromatography (SiO_2, 3:97 EtOAc:hexanes), the title compound **2.6m** (640 mg, 4.0 mmol) was obtained as a colorless oil in 73% yield.

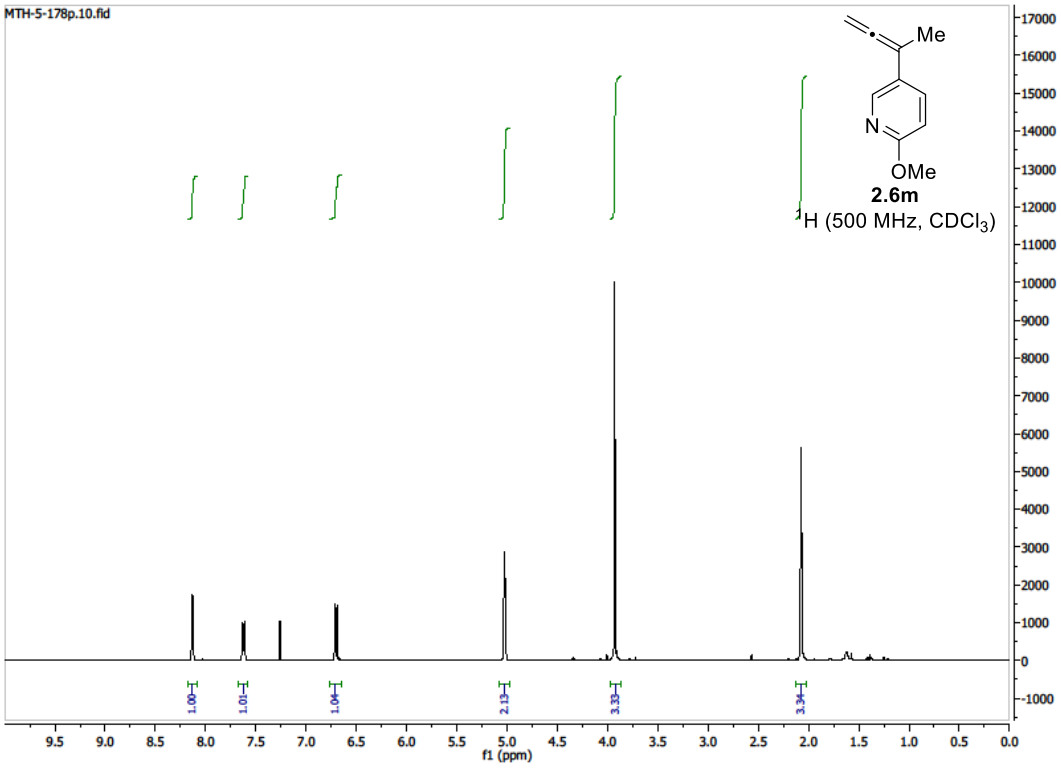
R_f = 0.41 (95:5 hexanes:EtOAc)

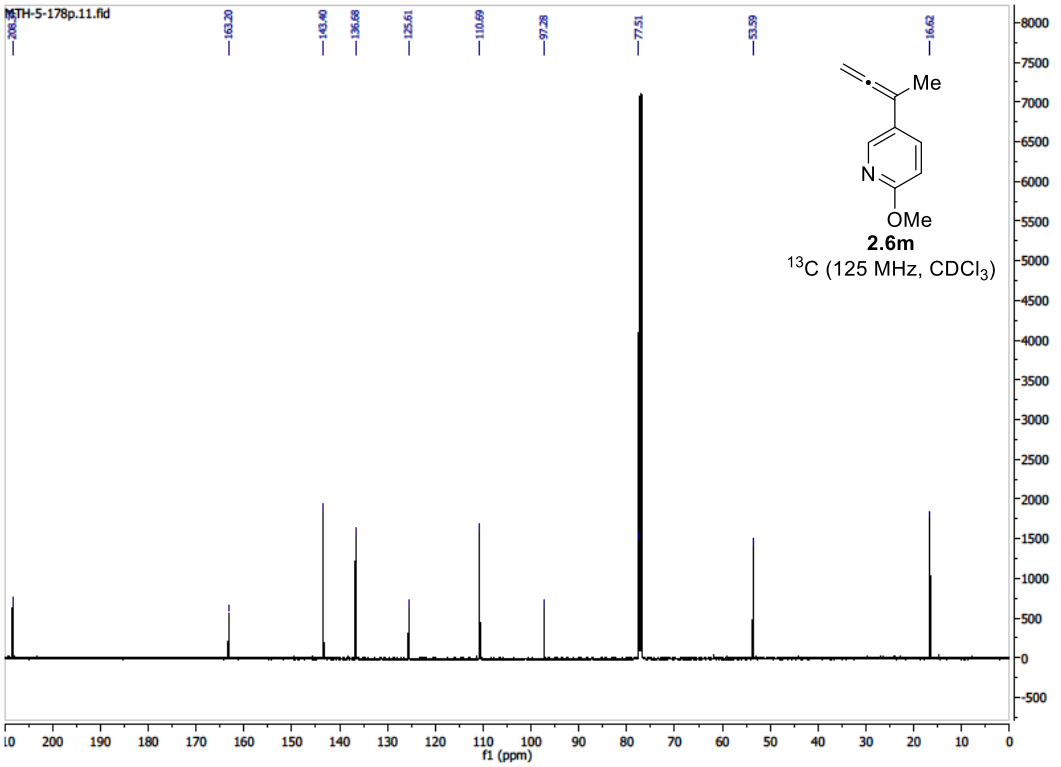
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 7.62 (d, *J* = 9.3 Hz, 1H), 6.70 (d, *J* = 9.3 Hz, 1H), 5.03 (q, *J* = 2.8 Hz, 2H), 3.93 (s, 3H), 2.08 (t, *J* = 2.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.4, 163.2, 143.4, 136.7, 125.6, 110.7, 97.3, 77.5, 53.6, 16.6.

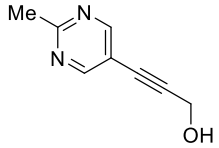
HRMS (CI+, *m/z*) for $C_{10}H_{11}NO$: calcd. = 162.0913; found = 162.0916.

FTIR (neat): 2950, 1725, 1661, 1602, 1493, 1263, 1022 cm^{-1}.


MTH-5-178p.10.fid
Me
N
OMe
2.6m
^{1}H (500 MHz, $CDCl_3$)
1.00
1.01
1.04
2.13
3.33
3.34
f1 (ppm)


MTH-5-178p.11.fid
163.20
143.40
136.68
125.61
110.69
97.28
77.51
53.59
16.62
Me
N
OMe
2.6m
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

3-(2-Methylpyrimidin-5-yl)prop-2-yn-1-ol (2.19n)



2.19n

To a stirred solution of 5-bromo-2-methylpyrimidine (2.60 g, 15 mmol) in DMF (15 mL) was added triethylamine (4.2 mL, 30 mmol) and propargyl alcohol (0.97 mL, 16.5 mmol). The solution was sparged for 10 minutes with Ar. Copper iodide (114 mg, 0.6 mmol) and bis(triphenylphosphine)palladium (II) dichloride (211 mg, 0.3 mmol) were added and the reaction mixture was stirred at 100 °C for 36 h. H_2O (100 mL) and ethyl acetate (100 mL) were added and the reaction mixture was filtered. The phases were separated and the aqueous layer washed with ethyl acetate (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 2:1 hexanes:EtOAc) to afford the title compound **2.19n** (0.79 g, 5.3 mmol) as a light yellow solid in 36% yield.

R_f = 0.1 (1:1 hexanes:EtOAc)

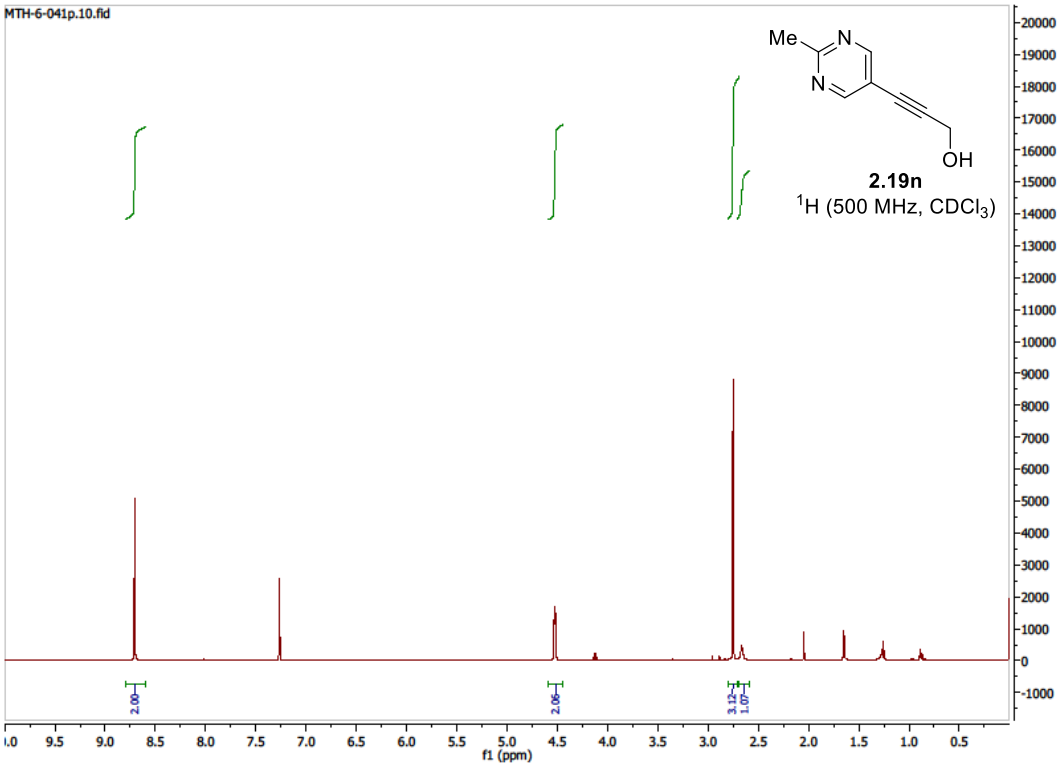
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.71 (s, 2H), 4.52 (d, *J* = 5.6 Hz, 2H), 2.75 (s, 3H), 2.67 (t, *J* = 5.6 Hz, 1H, O*H*).

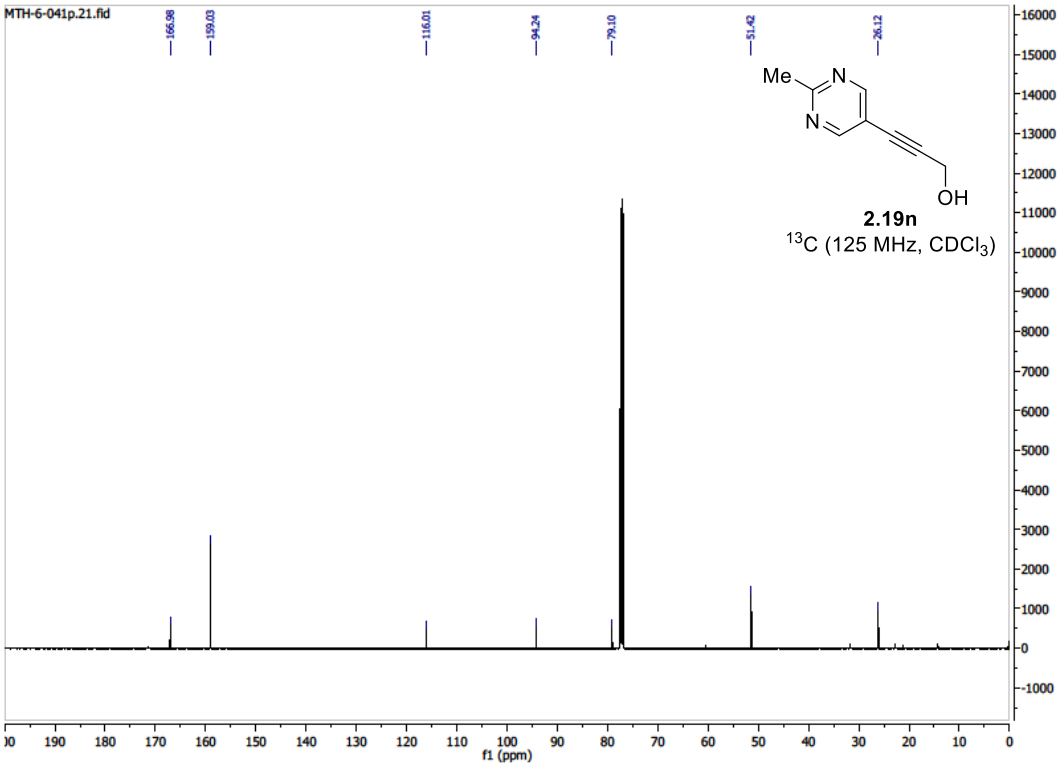
^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.0, 159.0, 116.0, 94.2, 79.1, 51.4, 26.1.

HRMS (ESI+H, *m/z*) for $C_8H_8N_2O$: calcd. = 149.0709; found = 149.0710.

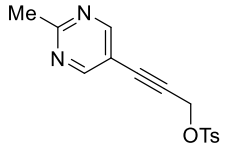
FTIR (neat): 3708, 3258, 2938, 2864, 2360, 1589, 1447, 1032, 744 cm^{-1}.

MP = 120-123 °C.


MTH-6-041p.10.fid
Me
N
N
OH
2.19n
^{1}H (500 MHz, $CDCl_3$)
2.00
2.06
3.12
1.07
f1 (ppm)


MTH-6-041p.21.fid
166.98
159.03
116.01
94.24
79.10
51.42
26.12
Me
N
N
OH
2.19n
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

3-(2-methylpyrimidin-5-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (2.20n)



2.20n

To a stirred solution of propargyl alcohol **2.19n** (0.74 g, 5.0 mmol) in Et_2O (7 mL) at 0 °C was added tosyl chloride (1.05 g, 5.5 mmol) followed by crushed potassium hydroxide (1.40 g, 25 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was poured onto ice water (30 mL) and diluted with Et_2O (30 mL). The phases were separated and the organic phase was washed with H_2O (2 x 30 mL). The combined aqueous phases were washed with Et_2O (2 x 30 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 1:1 hexanes:EtOAc) to afford the title compound **2.20n** (1.22 g, 4.1 mmol) as a light yellow solid in 81% yield.

R_f = 0.16 (1:1 hexanes : EtOAc)

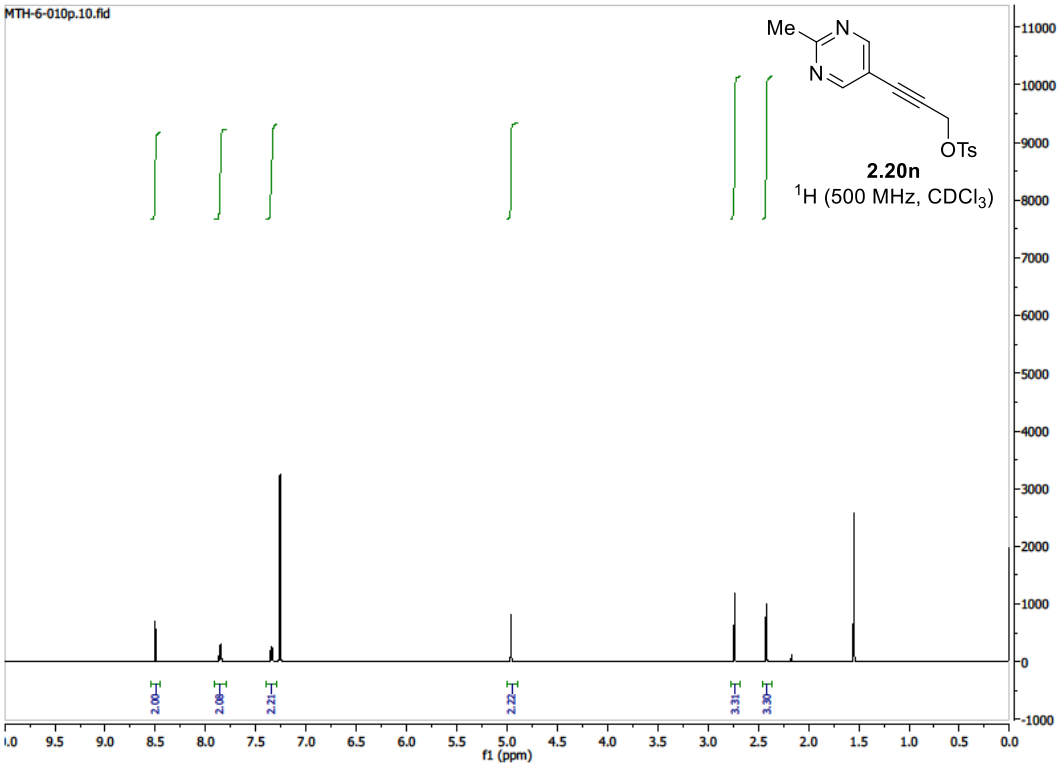
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.50 (s, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.96 (s, 2H), 2.73 (s, 3H), 2.42 (s, 3H).

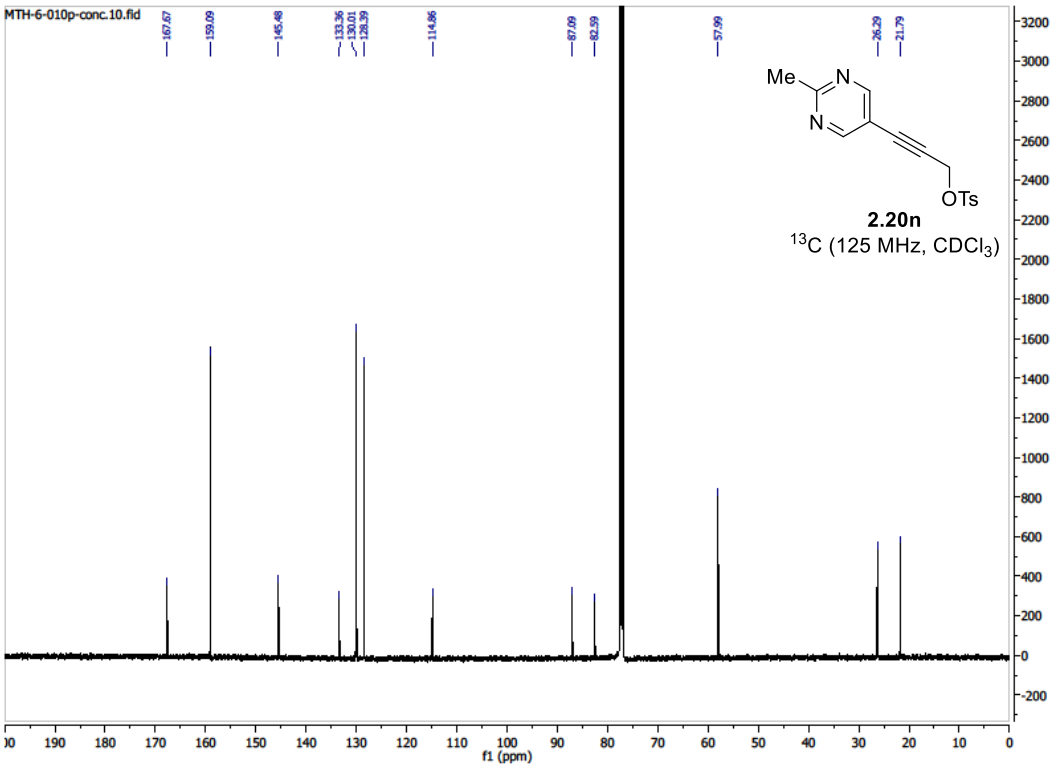
^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 159.1, 145.5, 133.4, 130.0, 128.4, 114.9, 87.1, 82.6, 58.0, 26.3, 21.8.

HRMS (Cl+, *m/z*) for $C_{15}H_{14}N_2O_3S$: calcd. = 303.0798; found = 303.0796.

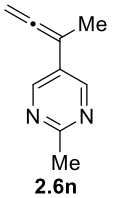
FTIR (neat): 3709, 2981, 2362, 1584, 1446, 1369, 1176, 939, 746 cm^{-1}.

MP = 105-107 °C.


MTH-6-010p.10.fid
Me
N
N
OTs
2.20n
^{1}H (500 MHz, $CDCl_3$)
2.00
2.08
2.21
2.22
3.31
3.30
f1 (ppm)


MTH-6-010p-conc.10.fid
167.67
159.09
145.48
133.36
130.01
128.39
114.86
87.09
82.59
57.99
26.29
21.79
Me
N
N
OTs
2.20n
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

5-(Buta-2,3-dien-2-yl)-2-methylpyrimidine (2.6n)



2.6n

To a stirred solution of propargyl tosylate **2.20n** (0.40 g, 1.3 mmol) and copper (I) bromide (37 mg, 0.3 mmol) in THF (2 mL) was added MeMgBr (3 M in Et_2O, 0.5 mL, 1.6 mmol) dropwise over 10 minutes. The reaction mixture was stirred for 1 hour at 25 °C. Saturated aqueous NH_4Cl solution (2 mL) and EtOAc (3 mL) were added and the phases were separated. The aqueous phase was washed with EtOAc (3 x 3 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 2:1 hexanes:EtOAc) to afford the title compound **2.6n** (113 mg, 0.78 mmol) as a light yellow solid in 65% yield.

R_f = 0.27 (2:1 hexanes : EtOAc)

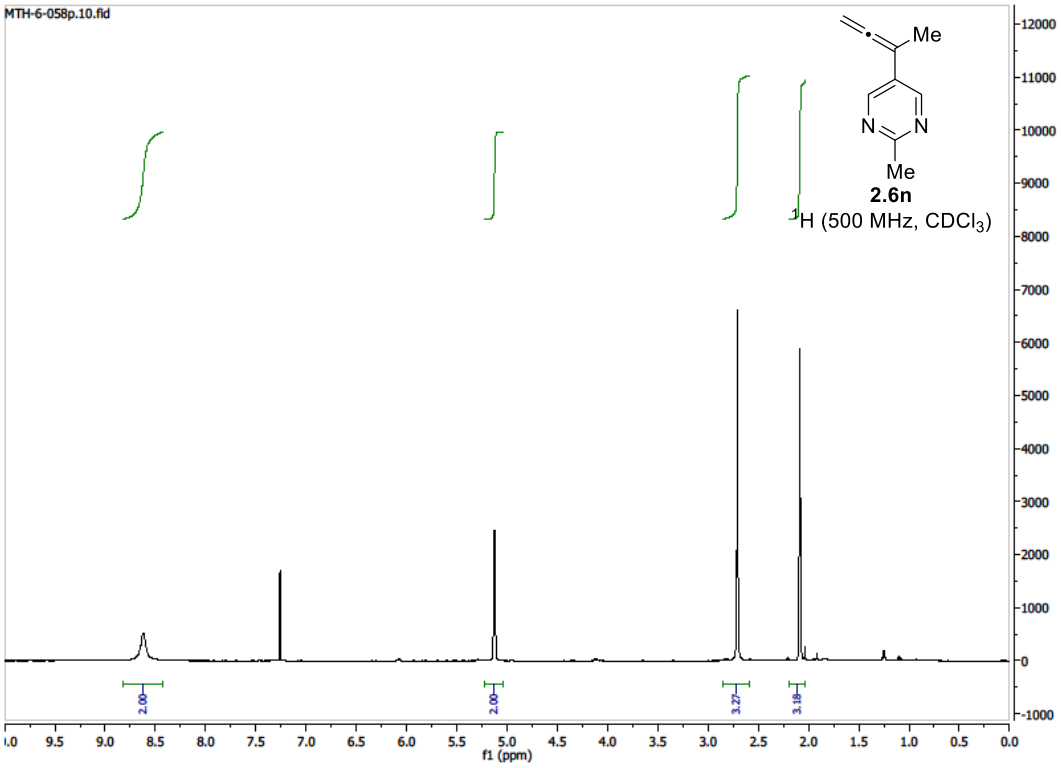
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.62 (s, 2H), 5.13 (q, *J* = 3.3 Hz, 2H), 2.71 (s, 3H), 2.09 (t, *J* = 3.3 Hz, 3H).

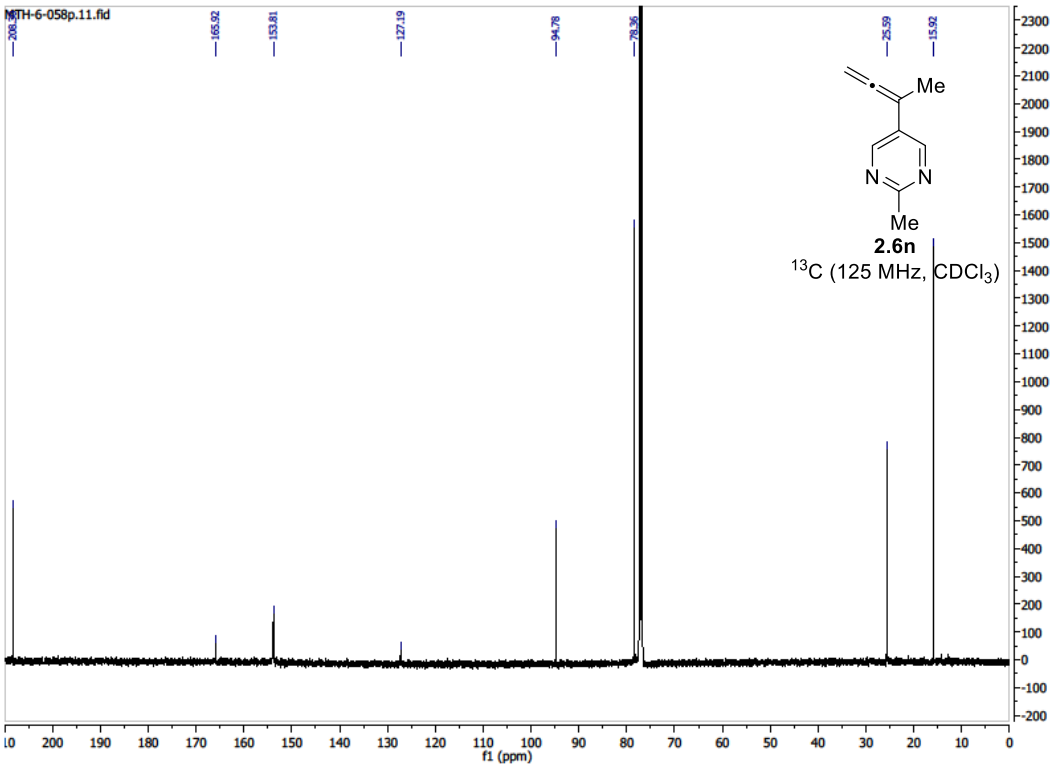
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.3, 165.9, 153.8, 127.2, 94.8, 78.4, 25.6, 15.9.

HRMS (ESI+, *m/z*) for $C_9H_{10}N_2$: calcd. = 147.0917; found = 147.0917.

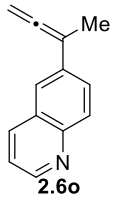
FTIR (neat): 2986, 1944, 1584, 1546, 1412, 1034, 858 cm^{-1}.

MP = 57-60 °C.


MTH-6-058p.10.fid
Me
N
N
Me
2.6n
^{1}H (500 MHz, $CDCl_3$)
2.00
2.00
3.27
3.18
f1 (ppm)


MTH-6-058p.11.fid
208.38
165.92
153.81
127.19
94.78
78.36
25.59
15.92
Me
N
N
Me
2.6n
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

6-(Buta-2,3-dien-2-yl)quinoline (2.6o)



2.6o

6-Bromoquinoline (1.08 mL, 8.0 mmol) was subjected to general described in **2.6j**.[56] Upon flash column chromatography (SiO_2, 1:3 EtOAc/hexanes), the title compound **2.6o** (0.65 g, 3.6 mmol) was obtained as a light yellow oil in 45 % yield.

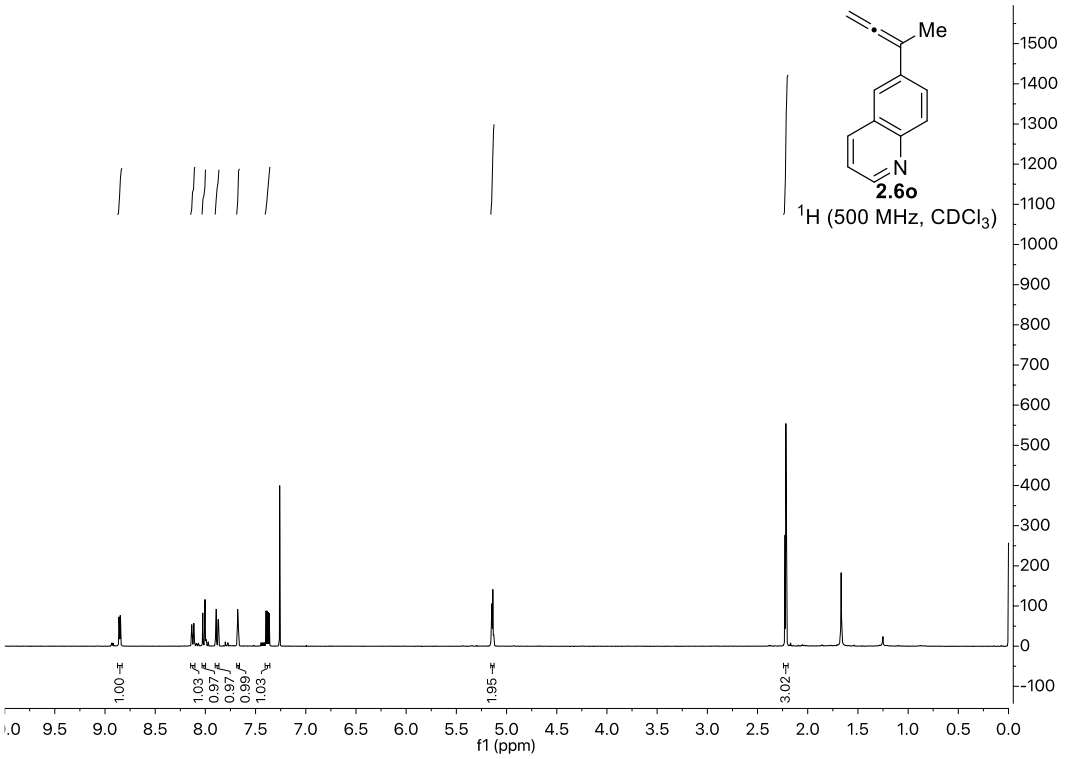
R_f = 0.29 (3:1 hexanes : EtOAc)

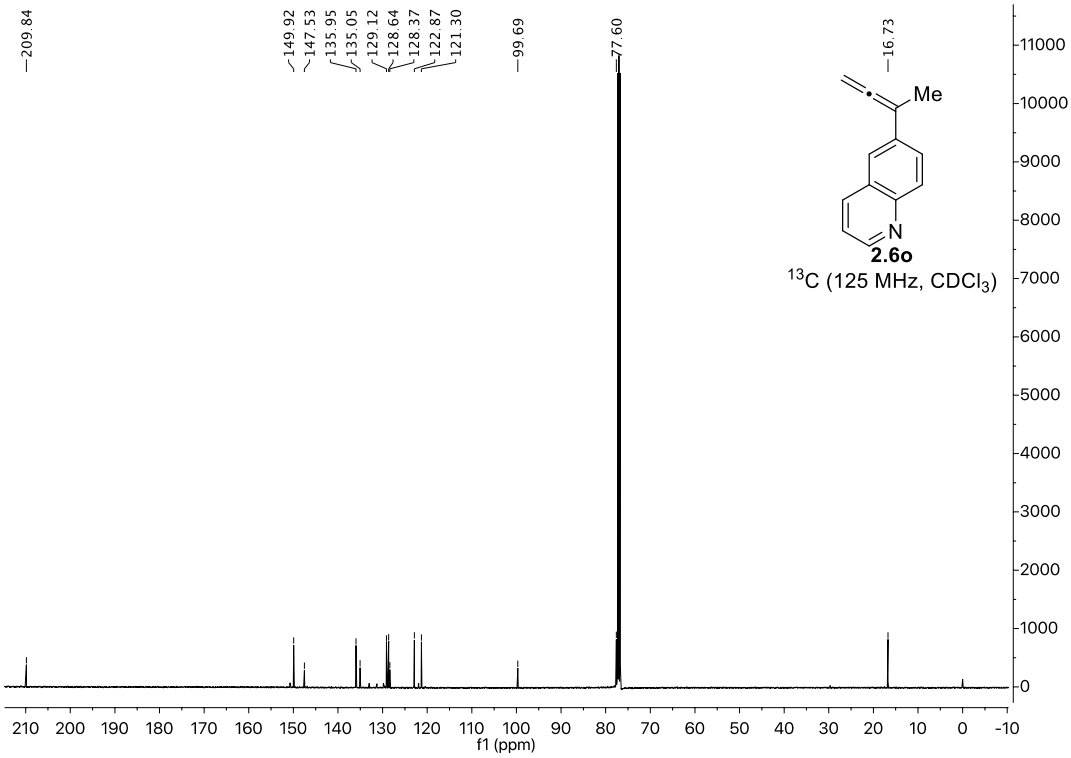
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.85 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.14 (q, *J* = 3.1 Hz, 2H), 2.22 (t, *J* = 3.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.8, 149.9, 147.5, 136.0, 135.1, 129.1, 128.6, 128.4, 122.9, 121.3, 99.7, 77.6, 16.7.

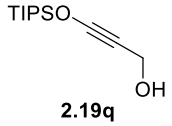
HRMS (ESI + H, *m/z*) for $C_{13}H_{11}N$: calcd. = 182.0964; found = 182.0968.

FTIR (neat): 2981, 1933, 1572, 1488, 1371, 1317, 953, 876, 830, 793, 771 cm^{-1}.


Me
N
2.6o
^{1}H (500 MHz, CDCl$_3$)
1.00
1.03
0.97
0.97
0.99
1.03
1.95
3.02
f1 (ppm)


209.84
149.92
147.53
135.95
135.05
129.12
128.64
128.37
122.87
121.30
99.69
77.60
16.73
Me
N
2.6o
^{13}C (125 MHz, CDCl$_3$)
f1 (ppm)

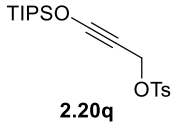
4-((Triisopropylsilyl)oxy)but-2-yn-1-ol (2.19q)



2.19q

To a stirred solution of propargyl alcohol (2.4 mL, 40 mmol) in CH_2Cl_2 (130 mL) at 0 °C was added imidazole (3.3 g, 48 mmol) followed by triisopropylchloride (9.4 mL, 44 mmol). The reaction mixture was stirred for 14 hours. Water (100 mL) was added and the phases were separated. The organic phase was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The silyl propargyl ether was dissolved in THF (40 mL) and cooled to -78 °C. *n*BuLi (2.5M in hexane, 19.2 mL, 48 mmol) was added and the reaction mixture was stirred at -78 °C for 10 minutes. The reaction mixture was warmed to 0 °C and stirred for 1 hour. The reaction mixture was cooled to -78 °C and paraformaldehyde (1.44 g, 48 mmol) was added in a single portion. The reaction mixture was allowed to warm to room temperature and stirred for 14 hours. Saturated aqueous NH_4Cl solution (50 mL) was added followed by EtOAc (100 mL). The phases were separated and the organic phase was washed with water (2 x 100 mL). The combined aqueous phases were washed with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude material **2.19q** was used in the following step without purification.

4-((Triisopropylsilyl)oxy)but-2-yn-1-yl 4-methylbenzenesulfonate (2.20q)



2.20q

To a stirred solution of propargyl alcohol **2.19q** (~40 mmol) in Et_2O (40 mL) at 0 °C was added tosyl chloride (6.1 g, 32 mmol) followed by crushed potassium hydroxide (11.2 g, 200 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was poured onto ice water (100 mL) and diluted with Et_2O (100 mL). The phases were separated and the organic phase was washed with H_2O (2 x 100 mL). The combined aqueous phases were washed with Et_2O (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 5:95 ethyl acetate:hexanes) to afford the title compound **2.20q** (10.3 g, 26 mmol) as a colorless oil in 65% yield over 3 steps.

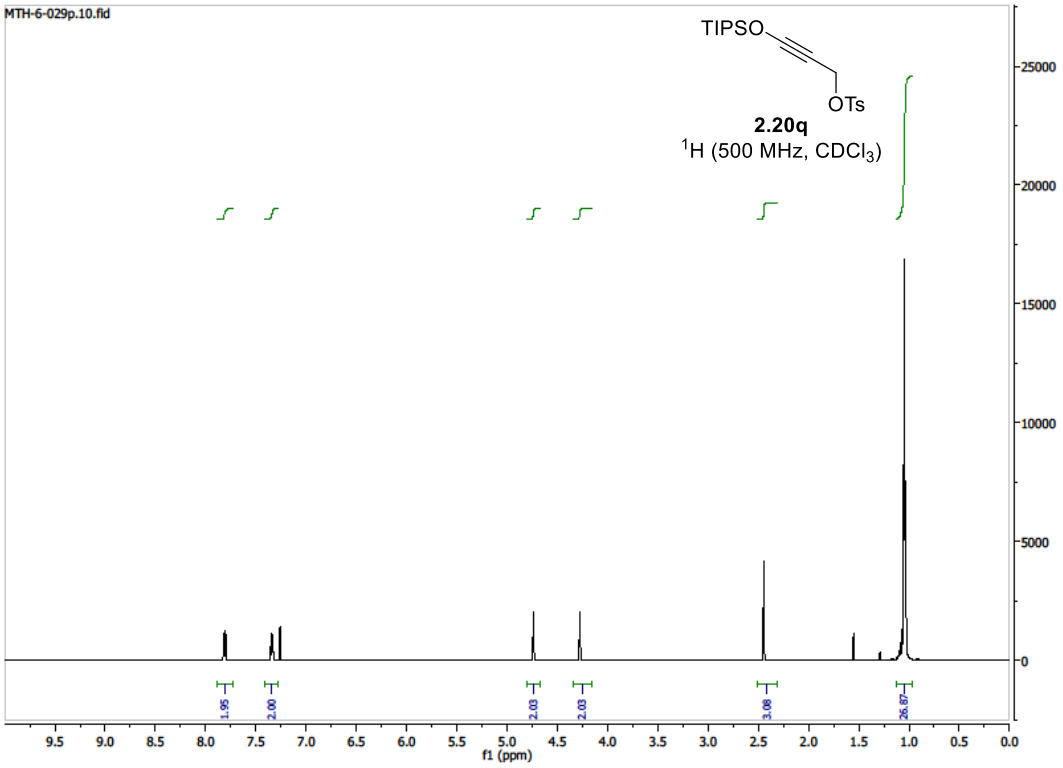
R_f = 0.41 (9:1 hexanes:EtOAc)

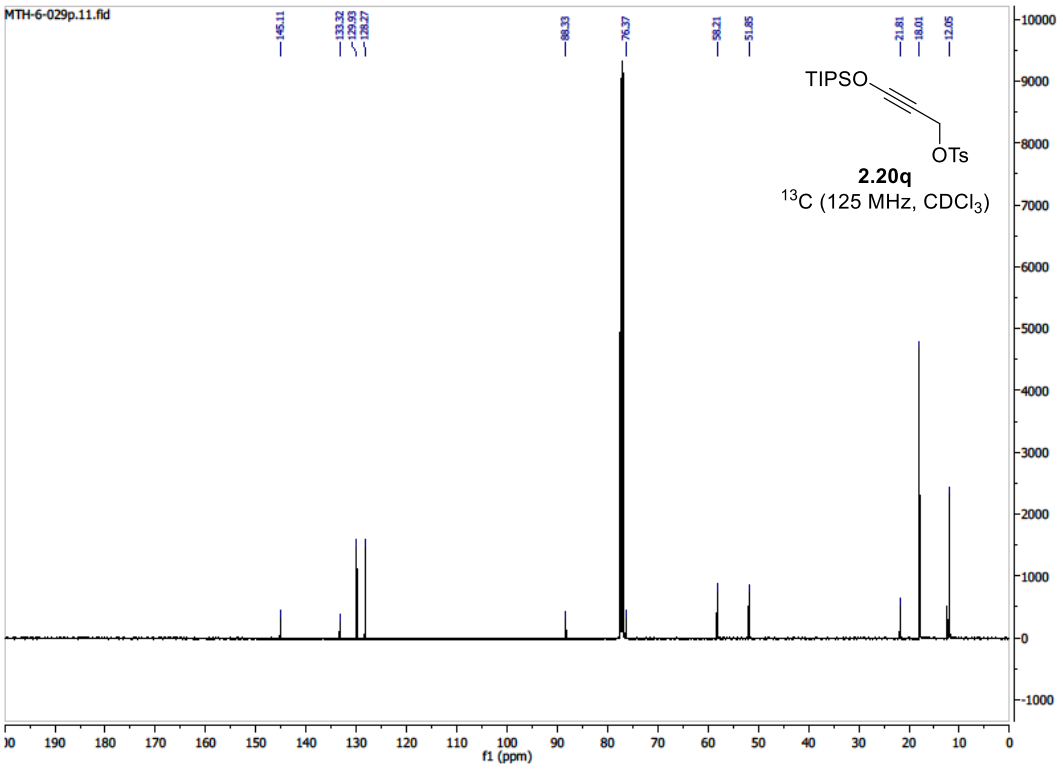
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 4.74 (s, 2H), 4.28 (s, 2H), 2.45 (s, 3H), 1.05 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.1, 133.3, 129.9, 128.3, 88.3, 76.4, 48.2, 51.9, 21.8, 18.0, 12.1.

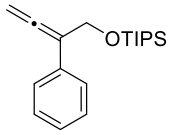
HRMS (ESI+NH_4, *m/z*) for $C_{20}H_{32}O_4SSi$: calcd. = 414.2129; found = 414.2135.

FTIR (neat): 3708, 2942, 2866, 2360, 1464, 1367, 1176, 1057, 946, 755, 665 cm^{-1}.


MTH-6-029p.10.fid
TIPSO
OTs
2.20q
^{1}H (500 MHz, $CDCl_3$)
1.95
2.00
2.03
2.03
3.08
26.87
f1 (ppm)


MTH-6-029p.11.fid
145.11
133.32
129.93
128.27
88.33
76.37
58.21
51.85
21.81
18.01
12.05
TIPSO
OTs
2.20q
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

Triisopropyl((2-phenyl-buta-2,3-dien-1-yl)oxy)silane (2.6q)



2.6q

To a stirred solution of copper (I) bromide (1.43 g, 10 mmol) in THF (20 mL) was added PhMgBr (3M in Et_2O, 4 mL, 12 mmol) over 5 minutes. The reaction mixture was stirred for 5 minutes. In a separate flask propargyl tosylate **2.20q** (3.97 g, 10 mmol) was dissolved in THF (20 mL). The prepared nucleophile was added to this second flask dropwise over 10 minutes and the reaction mixture was stirred for 1 hour. Saturated aqueous NH_4Cl solution (50 mL) was added followed by EtOAc (50 mL). The phases were separated and the organic phase was washed with water (2 x 50 mL). The combined aqueous phases were washed with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, hexanes) to afford the title compound **2.6q** (2.36 g, 7.9 mmol) as a colorless oil in 79% yield. Note: The use of stoichiometric copper (I) bromide was essential to minimize the formation of the inseparable isomeric alkyne through S_N2 attack.

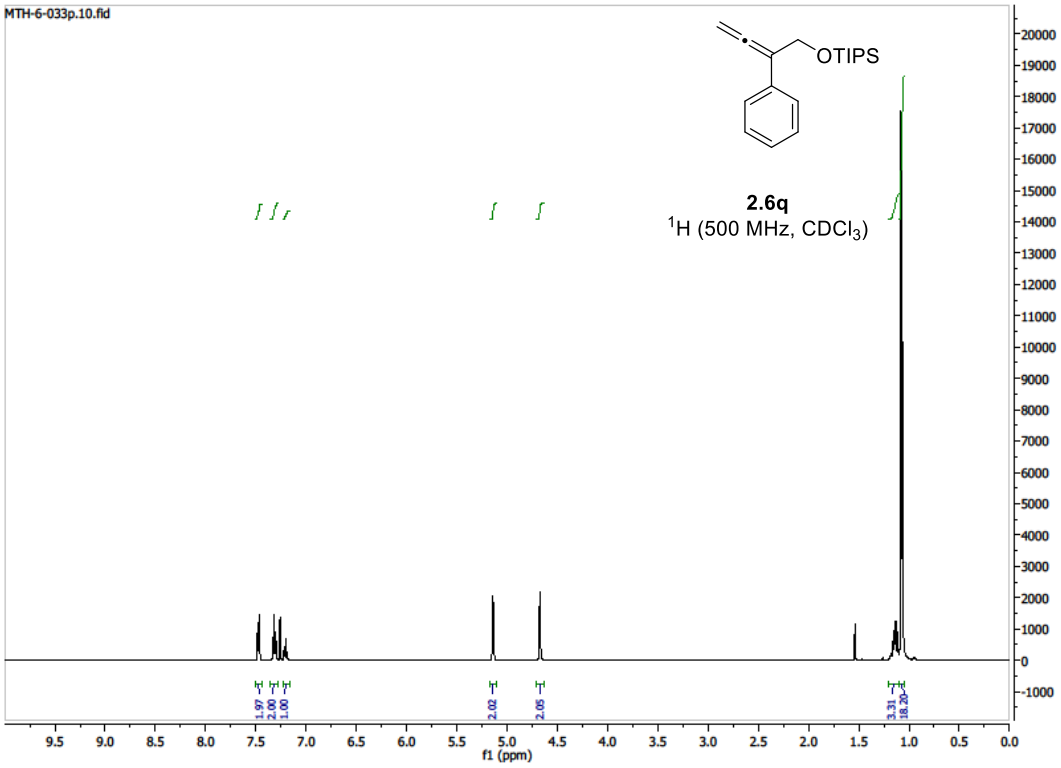
R_f = 0.29 (hexanes)

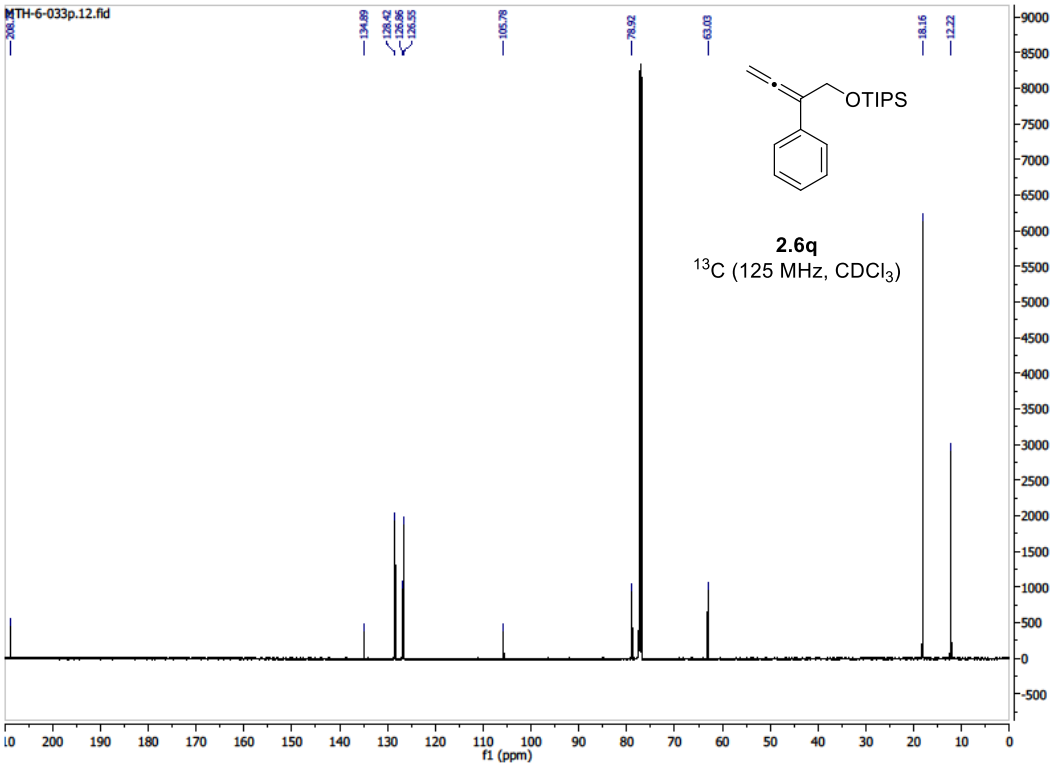
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.14 (t, *J* = 2.8 Hz, 2H), 4.68 (t, *J* = 2.8 Hz, 2H), 1.13 (m, 3H), 1.07 (d, *J* = 6.5 Hz, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7, 134.9, 128.4, 126.9, 126.6, 105.8, 78.9, 63.0, 18.2, 12.2.

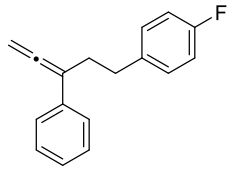
HRMS (ESI+H, *m/z*) for $C_{19}H_{30}OSi$: calcd. = 303.2139; found = 303.2140.

FTIR (neat): 2943, 2867, 1707, 1494, 1247, 10098, 1026, 883, 688 cm^{-1}.


MTH-6-033p.10.fid
OTIPS
2.6q
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


MTH-6-033p.12.fid
OTIPS
2.6q
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

1-Fluoro-4-(3-phenyl-4l5-penta-3,4-dien-1-yl)benzene (2.6t)



2.6t

Magnesium turnings (108 mg, 4.5 mmol) were placed into a 3-necked flask equipped with a reflux condenser. THF (6 mL) was added followed by a single crystal of iodine and the reaction mixture was stirred until the solution decolorized. 4-Fluorophenethyl bromide (910 mg, 4.5 mmol) was added and the reaction mixture was heated until it began to reflux. The heat was removed and the reaction mixture was stirred until the reflux ended. In a separate flask, 3-phenyl-2-propyn-1-ol tosylate[49] (860 mg, 3 mmol) and copper (I) bromide (43 mg, 0.3 mmol) were dissolved in THF (6 mL). The Grignard reagent was transferred to this flask through a cannula and the reaction mixture was stirred at room temperature for 1 hour. Saturated aqueous NH_4Cl solution (10 mL) was added followed by EtOAc (10 mL). The phases were separated and the organic phase was washed with water (2 x 10 mL). The combined aqueous phases were washed with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, hexanes) to afford the title compound **2.6t** (0.48 g, 2.0 mmol) as a colorless oil in 67% yield as a 4:1 mixture of allene:alkyne.

R_f = 0.37 (hexanes)

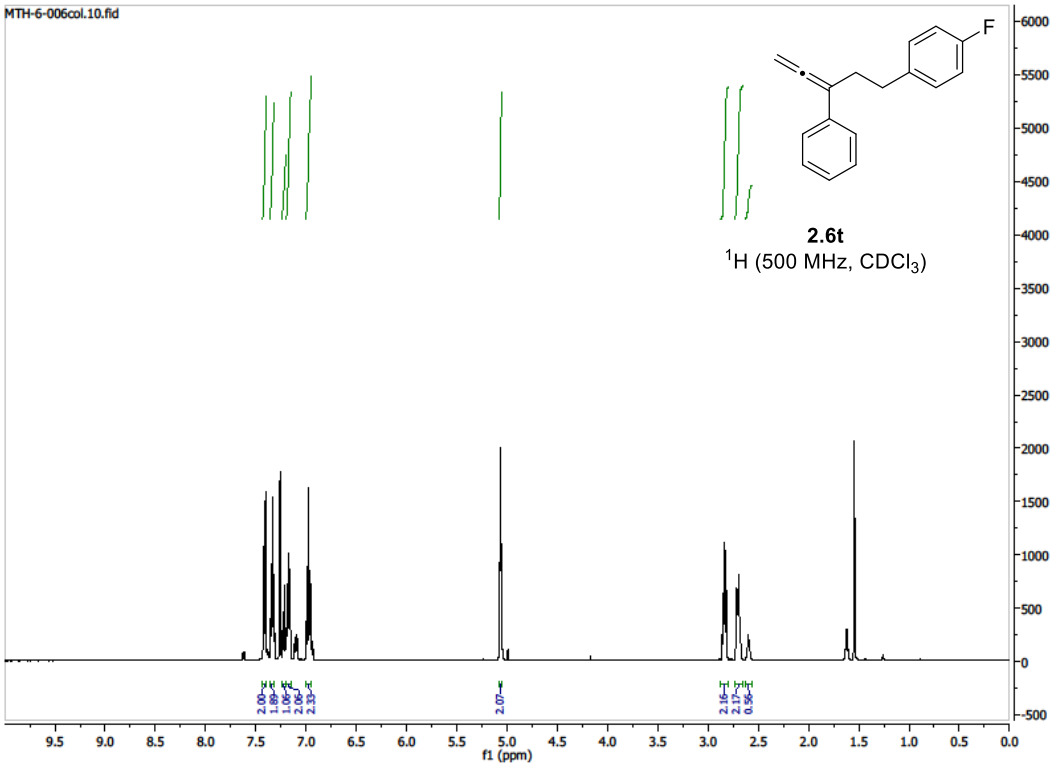
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 5.8, 8.5 Hz, 2H), 6.98 (dd, *J* = 8.5, 8.5 Hz, 2H), 5.07 (t, *J* = 3.2 Hz, 2H), 2.84 (m, 2H), 2.70 (m, 2H).

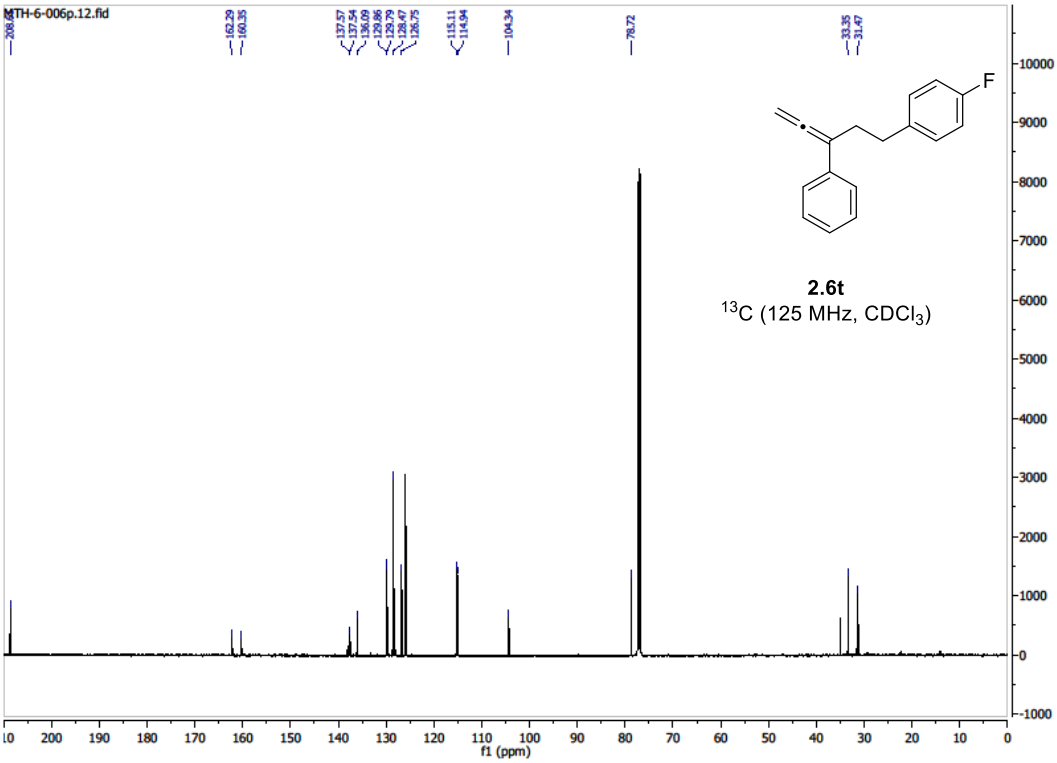
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.6, 161.4 (d, *J* = 240 Hz), 137.6 (d, *J* = 3 Hz), 136.1, 129.8 (d, *J* = 8 Hz), 128.5, 126.8, 125.9, 115.0 (d, *J* = 21 Hz), 104.3, 78.7, 33.4, 31.5.

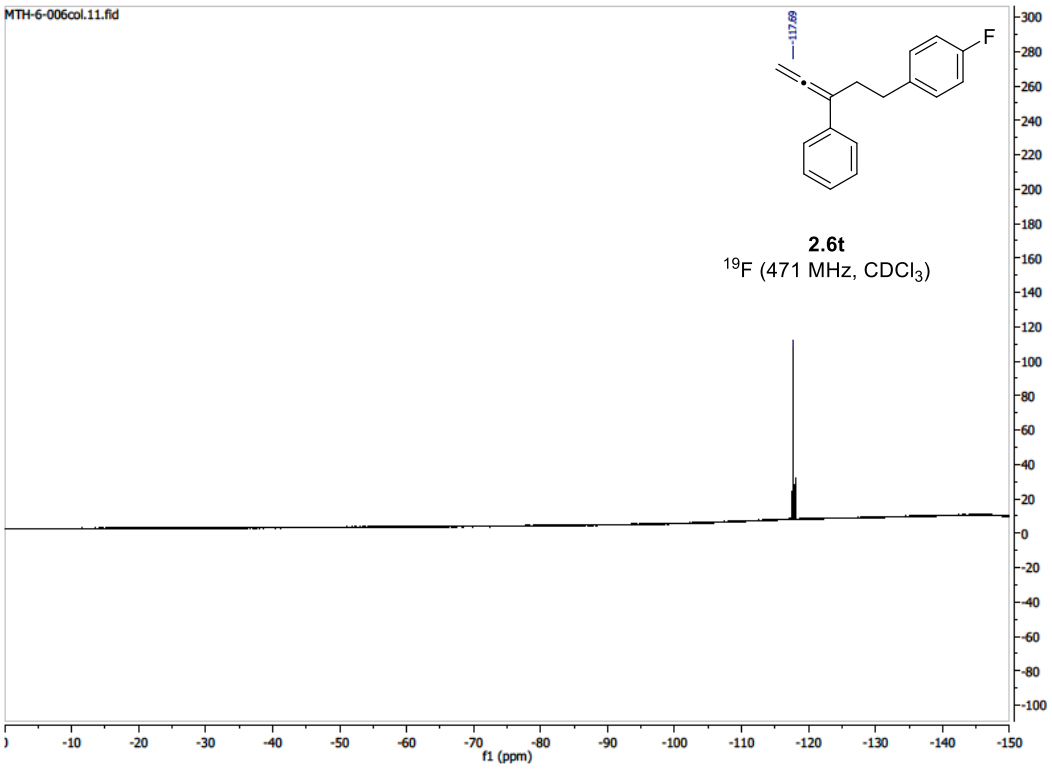
^{19}F NMR (470 MHz, $CDCl_3$) δ: -117.7 (tt, *J* = 5.7, 8.5 Hz).

HRMS (CI+, *m/z*) for $C_{17}H_{14}F$: calcd. = 237.1080; found = 237.1083.

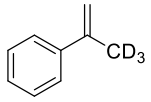
FTIR (neat): 2928, 1940, 1723, 1509, 1220, 1157, 824, 759 cm^{-1}.


MTH-6-006col.10.fid
F
2.6t
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


MTH-6-006p.12.fid
F
2.6t
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)


MTH-6-006col.11.fid
-117.69
F
2.6t
^{19}F (471 MHz, $CDCl_3$)
f1 (ppm)

(Prop-1-en-2-yl-3,3,3-d_3)benzene (*deuterio*-2.17a)

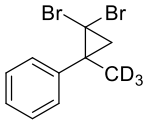


deuterio-**2.17a**

Acetophenone-β,β,β-d_3 (1.17 mL, 10 mmol) was subjected to general procedure H. Upon flash column chromatography (SiO_2, hexanes), the title compound *deuterio*-**2.17a** (0.98 g, 8.1 mmol) was obtained as a clear oil in 81% yield. Note: Keeping the reaction mixture at 0 °C throughout this reaction was essential to avoid H-D exchange.

The data reported was consistent with literature data.[60]

(2,2-dibromo-1-(methyl-d$_3$)cyclopropyl)benzene (*deuterio*-2.18a)



deuterio-**2.18a**

Styrene *deuterio*-**2.17a** (0.98 g, 8.1 mmol) was subjected to general procedure I. Upon flash column chromatography (SiO_2, hexanes), the title compound *deuterio*-**2.18a** (1.79 g, 6.1 mmol) was obtained as a clear oil in 75% yield.

R_f = 0.44 (hexanes)

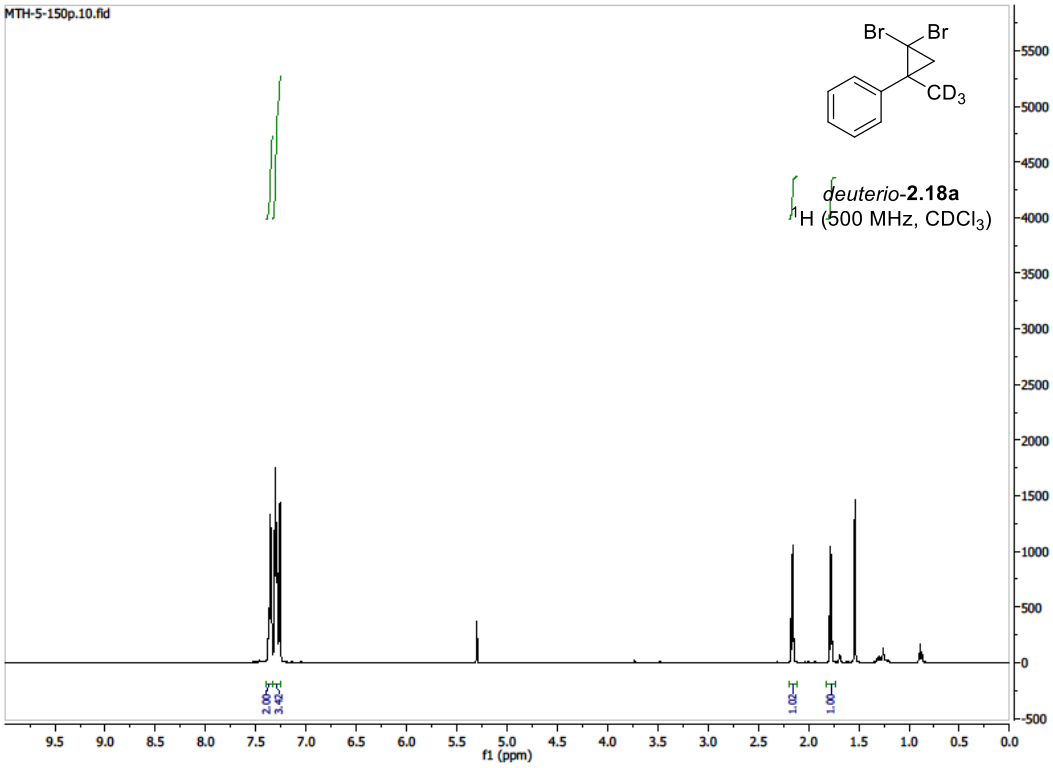
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H), 7.30 (m, 3H), 2.16 (d, *J* = 8.6 Hz, 1H), 1.78 (d, *J* = 8.6 Hz, 1H).

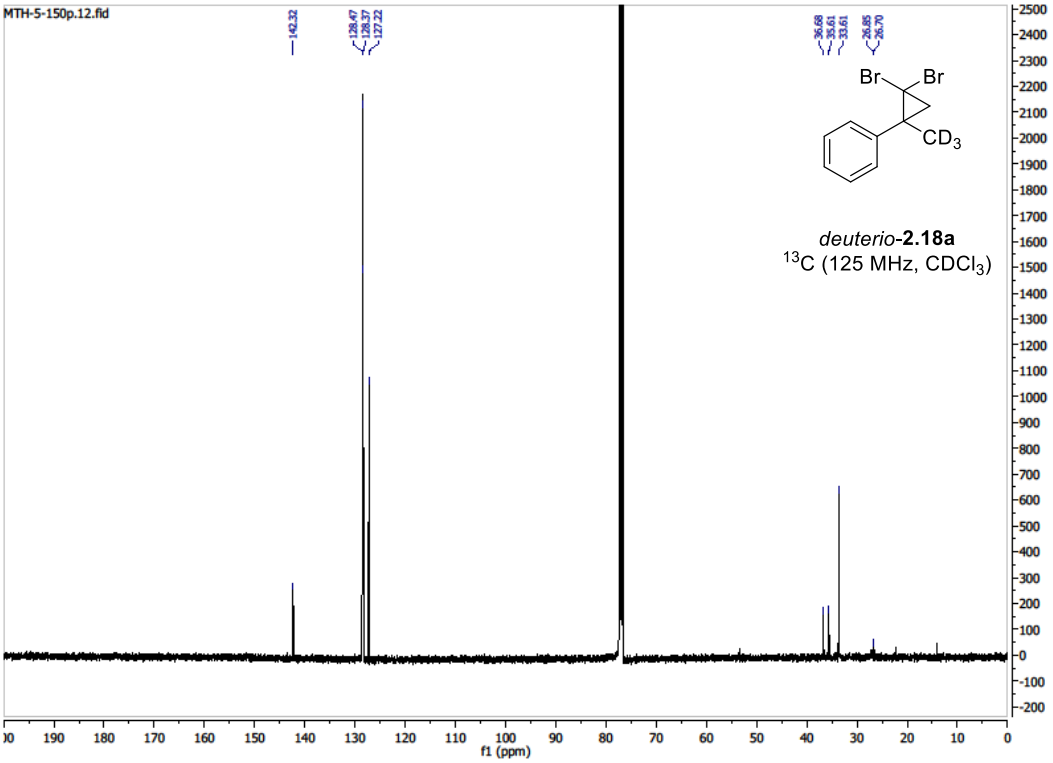
^{2}H NMR (500 MHz, $CDCl_3$) δ: 1.63

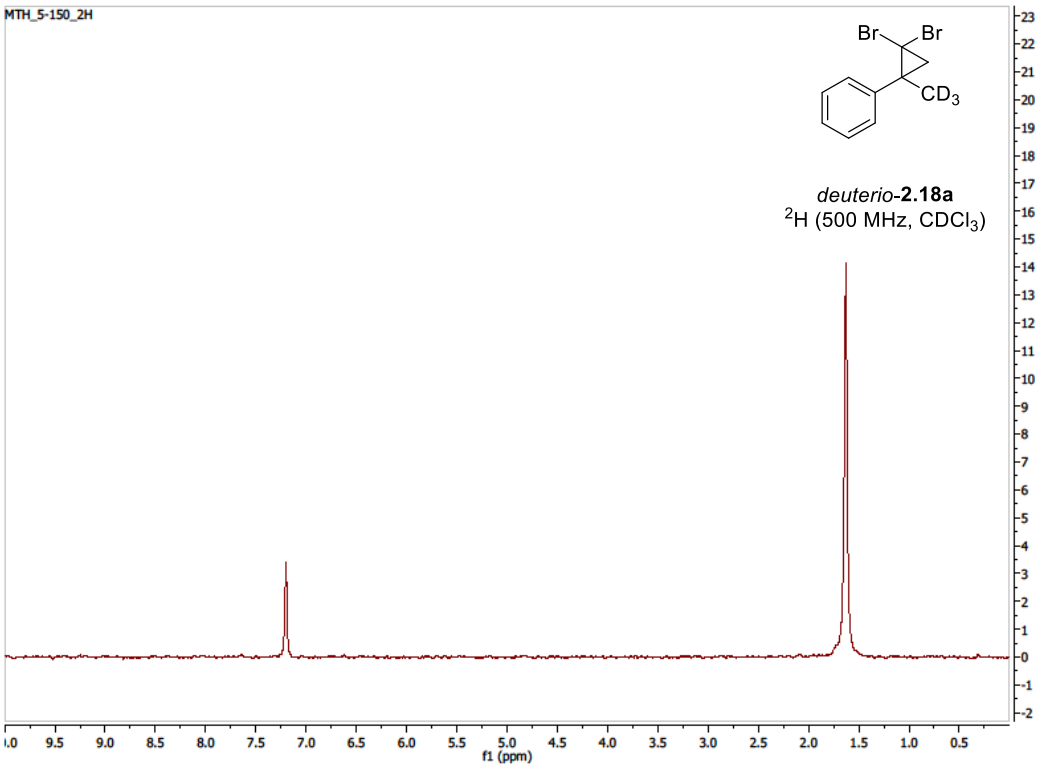
^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.3, 128.5, 128.4, 127.2, 36.7, 35.6, 33.6, 26.8 (m).

HRMS (Cl+, *m/z*) for $C_{10}H_8D_3Br_2$: calcd. = 291.9416; found = 291.9416.

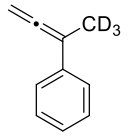
FTIR (neat): 3058, 3027, 2925, 2360, 1495, 1446, 1427, 1067, 1017, 749 cm^{-1}.


MTH-5-150p.10.fid
Br
Br
CD3
deuterio-2.18a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-150p.12.fid
142.32
138.47
128.57
127.22
36.68
33.61
33.61
26.85
26.70
Br
Br
CD3
deuterio-2.18a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH_5-150_2H
Br
Br
CD3
deuterio-2.18a
2H (500 MHz, CDCl3)
f1 (ppm)

(Buta-2,3-dien-2-yl-1,1,1-d$_3$)benzene (*deuterio*-2.6a)



deuterio-**2.6a**

1,1-disubstituted cyclopropane *deuterio*-**2.18a** (1.36 g, 4.6 mmol) was subjected to general procedure C. Upon flash column chromatography (SiO_2, pentane), the title compound *deuterio*-**2.6a** (0.53 g, 4.0 mmol) was obtained as a clear oil in 87% yield.

R$_f$ = 0.47 (hexanes)

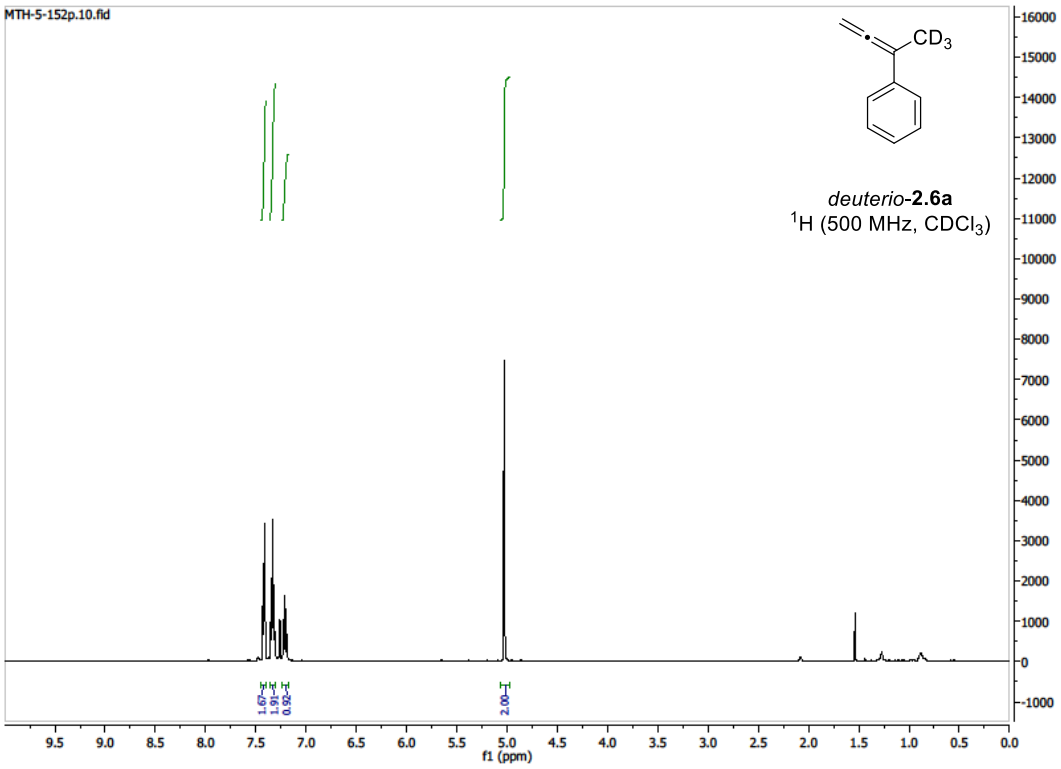
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 8.4 Hz, 1H), 5.03 (s, 2H).

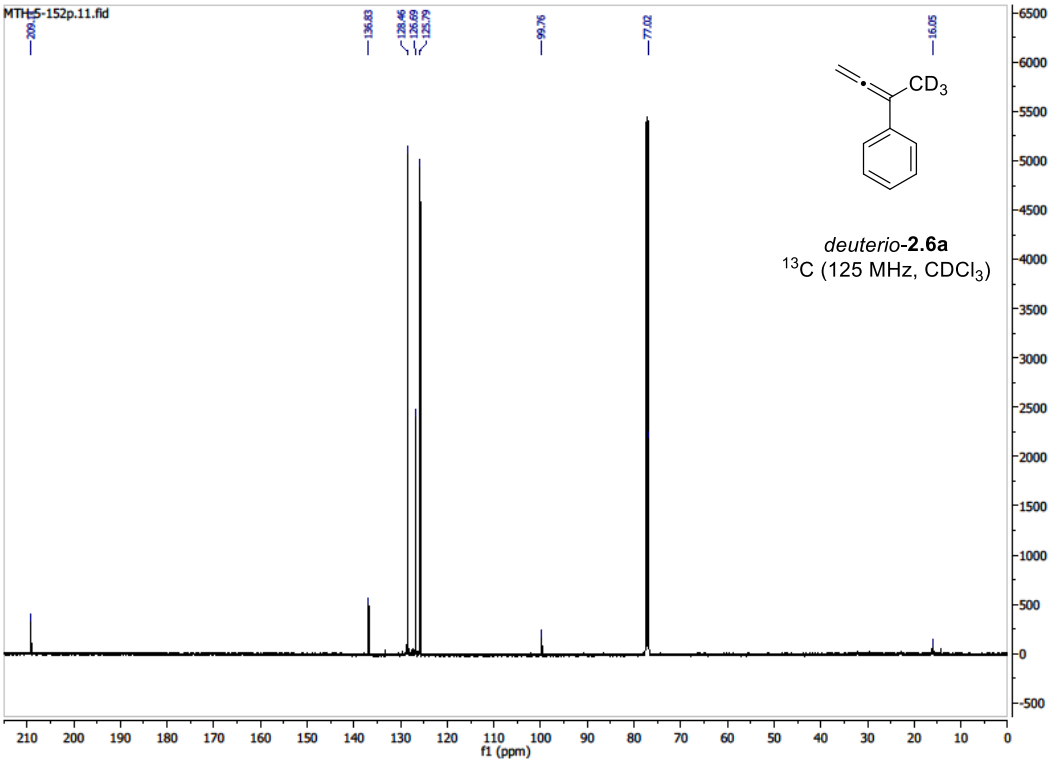
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.1, 136.8, 128.5, 126.7, 125.8, 99.8, 77.0, 16.1 (m).

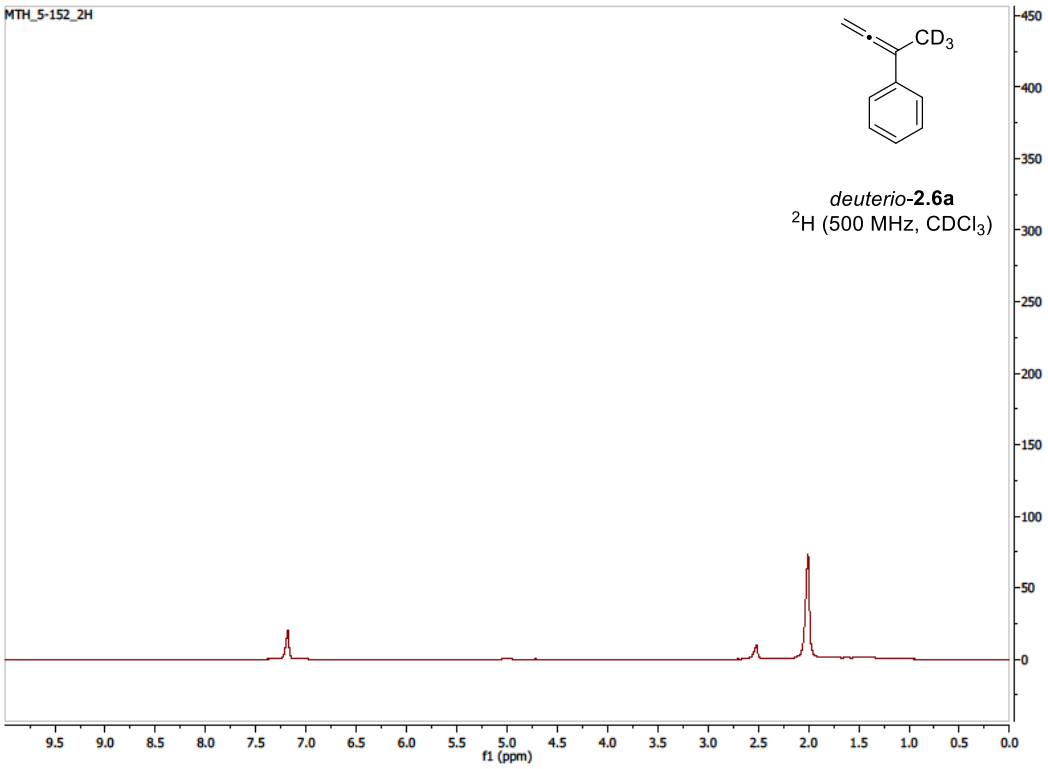
^{2}H NMR (500 MHz, $CDCl_3$) δ: 2.01.

HRMS (CI+, *m/z*) for $C_{10}H_6D_3$: calcd. = 132.0893; found = 132.888.

FTIR (neat): 3029, 2973, 1938, 1724, 1680, 1494, 1449, 1267, 1033, 758, 695 cm^{-1}.

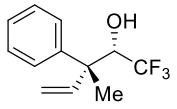

MTH-5-152p.10.fid
CD3
deuterio-2.6a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-152p.11.fid
209.15
136.83
128.46
126.69
125.79
99.76
77.02
16.05
CD3
deuterio-2.6a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH_5-152_2H
CD3
deuterio-2.6a
2H (500 MHz, CDCl3)
f1 (ppm)

2.5.4.3 Procedures and Spectral Data for Coupling Products of Fluoral and 1,1-Disubstituted Allenes 2.8[a–u]

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-phenylpent-4-en-2-ol (2.8a)



2.8a

1,1-Disubstituted allene **2.6a** (52 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 4:96 EtOAc:hexanes), the title compound **2.8a** (35.7 mg, 0.16 mmol, 17:1 dr) was obtained as a yellow oil in 78% yield. Note: This reaction was repeated on 2 mmol scale using $[Ir(cod)Cl]_2$ (1 mol%) and (*R*)-PhanePhos (2 mol%) to afford the product **2.8a** in 71% yield and 17:1 dr.

R_f = 0.41 (90:10 hexanes : EtOAc)

^{1}H NMR (500 MHz, CDCl3) δ: 7.40-7.34 (m, 4H), 7.26 (m, 1H), 6.39 (dd, J = 11.1, 17.8 Hz, 1H), 5.36 (d, J = 11.1 Hz, 1H), 5.20 (d, J = 17.8 Hz, 1H), 4.39 (dq, J = 6.0, 7.9 Hz, 1H), 2.19 (d, J = 6.0 Hz, 1H, OH), 1.57 (s, 3H).

^{13}C NMR (125 MHz, CDCl3) δ: 143.8, 140.8, 128.7, 127.1, 127.0, 126.2 (q, J = 285 Hz), 124.0, 76.0 (q, J = 26.0 Hz), 47.5, 21.1 (q, J = 2.7 Hz).

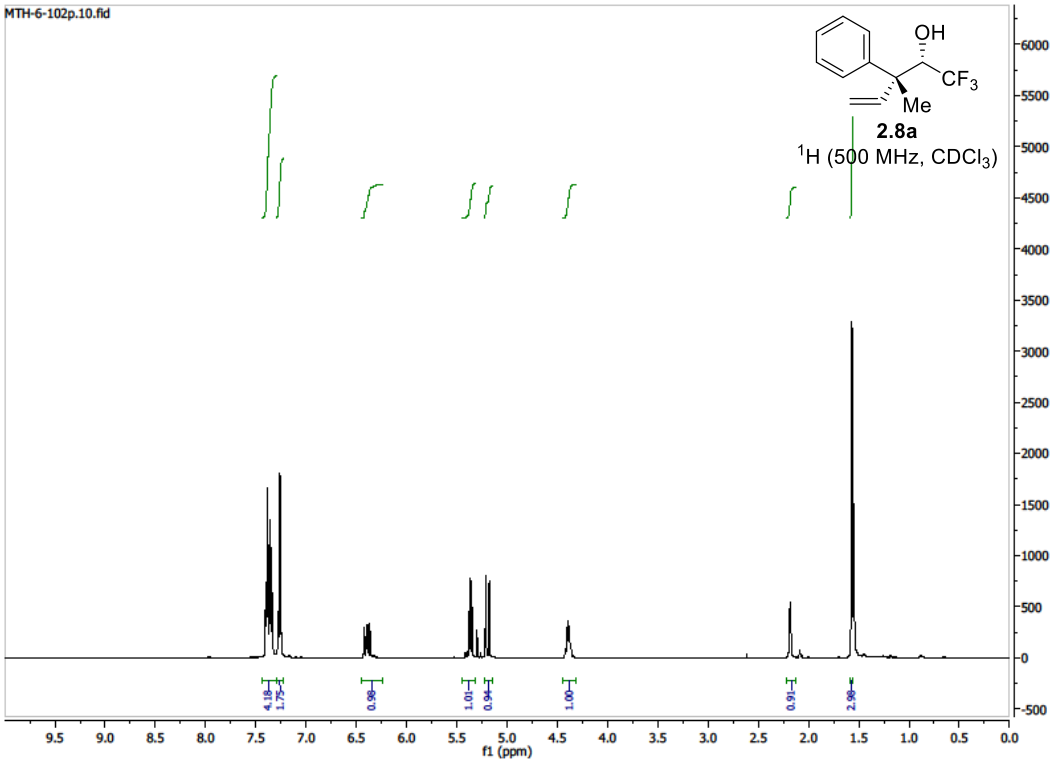
^{19}F NMR (470 MHz, CDCl3) δ: -70.7 (d, J = 7.4 Hz).

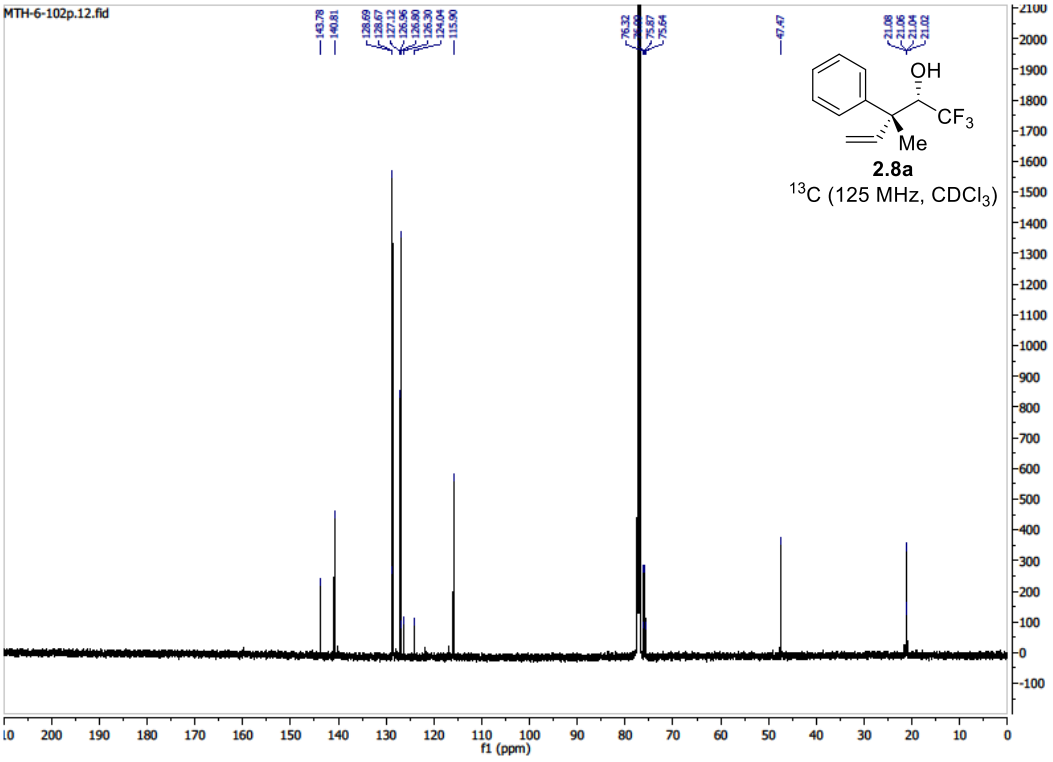
HRMS (CI+, m/z) for C12H13OF3: calcd. = 230.0918; found = 230.0922.

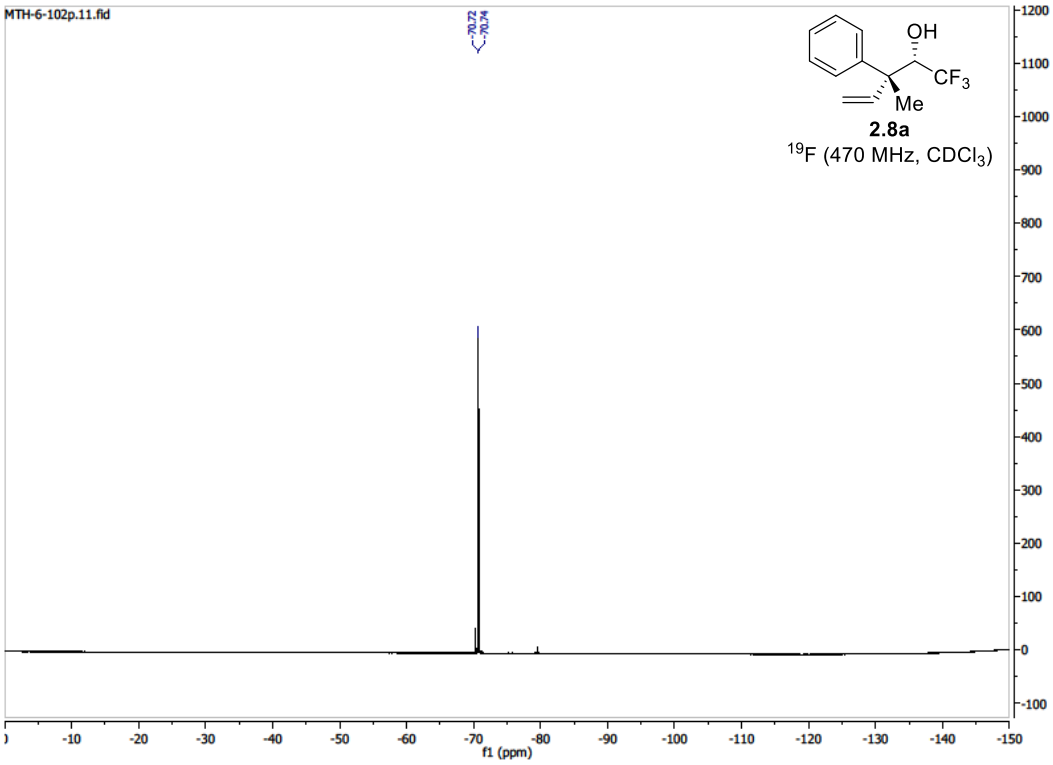
FTIR (neat): 3459, 2993, 2363, 1496, 1446, 1271, 1156, 1122, 926, 762, 701 cm-1.

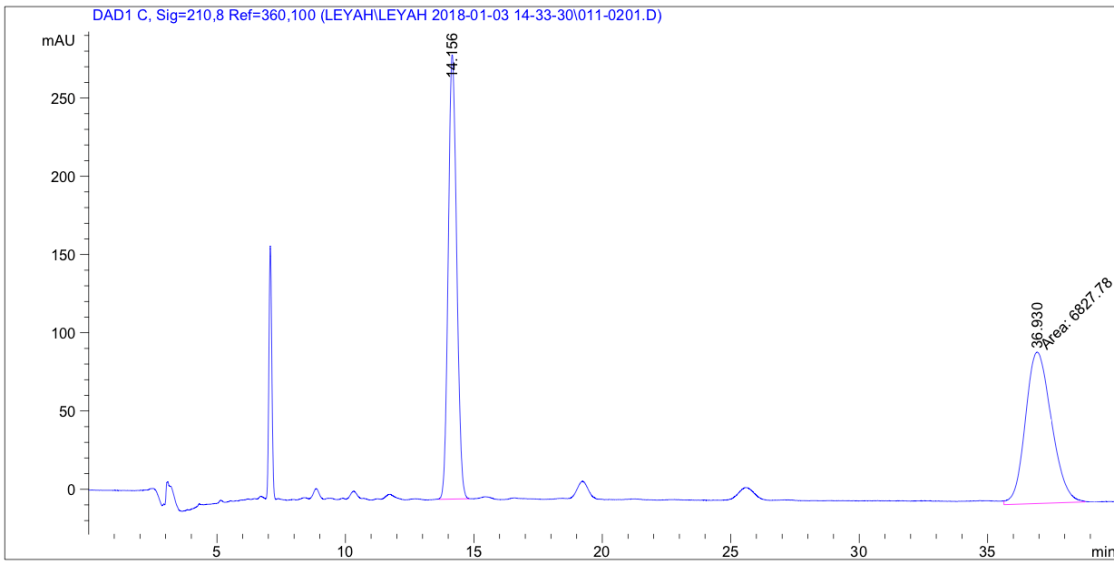
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -4.5 (c = 1.0, CHCl3).

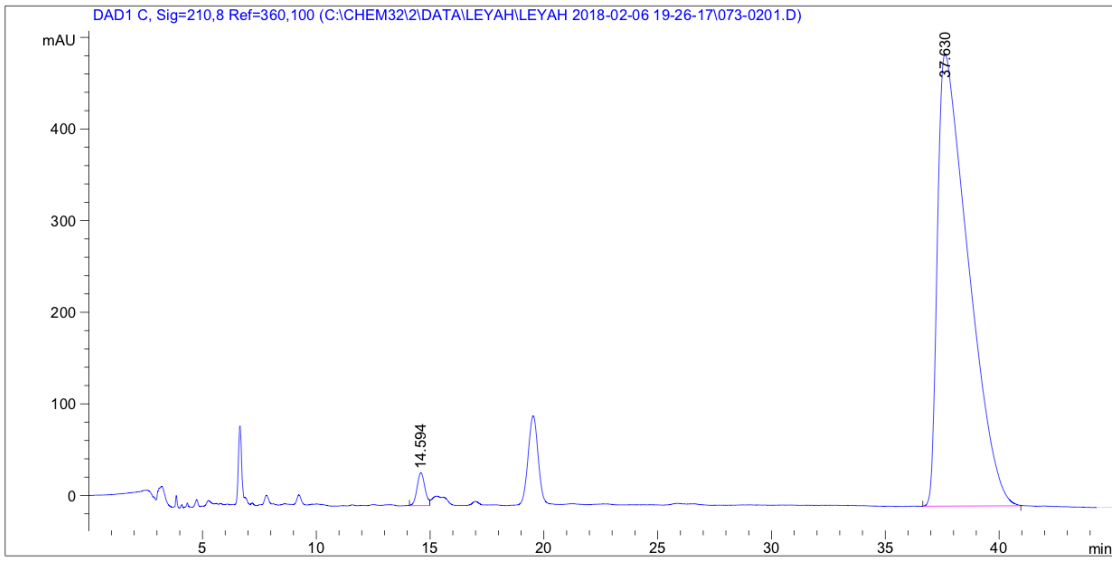

MTH-6-102p.10.fid
OH
CF3
Me
2.8a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-102p.12.fid
OH
CF3
Me
2.8a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-102p.11.fid
-70.72
-70.74
OH
CF3
Me
2.8a
19F (470 MHz, CDCl3)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

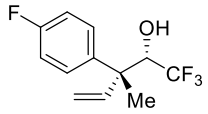


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.156	BB	0.3543	6482.22266	283.96756	48.7019
2	36.930	MM	1.1765	6827.77979	96.72146	51.2981



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.594	BV	0.3640	861.93768	35.91236	1.8278
2	37.630	BB	1.2622	4.62951e4	493.59952	98.1722

(2*S*,3*R*)-1,1,1-trifluoro-3-(4-fluorophenyl)-3-methylpent-4-en-2-ol (2.8b)



2.8b

1,1-Disubstituted allene **2.6b** (59.3 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:10 EtOAc/hexanes), the title compound **2.8b** (40.2 mg, 0.16 mmol, 19:1 dr) was obtained as a light yellow oil in 81% yield.

R_f = 0.4 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 2H), 7.03 (m, 2H), 6.35 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.35 (d, *J* = 10.9 Hz, 1H), 5.17 (d, *J* = 17.6 Hz, 1H), 4.33 (dq, *J* = 5.3, 1.8 Hz, 1H), 2.22 (d, *J* = 5.4 Hz, 1H), 1.56 (q, *J* = 1.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.6 (d, *J* = 246.5 Hz), 140.8, 139.2 (d, *J* = 3.2 Hz), 128.6 (d, *J* = 7.9 Hz), 125.0 (q, *J* = 283.5 Hz), 115.8, 115.2 (d, *J* = 21.2 Hz), 75.7 (q, *J* = 28.1 Hz), 46.9, 21.0 (q, *J* = 2.6 Hz).

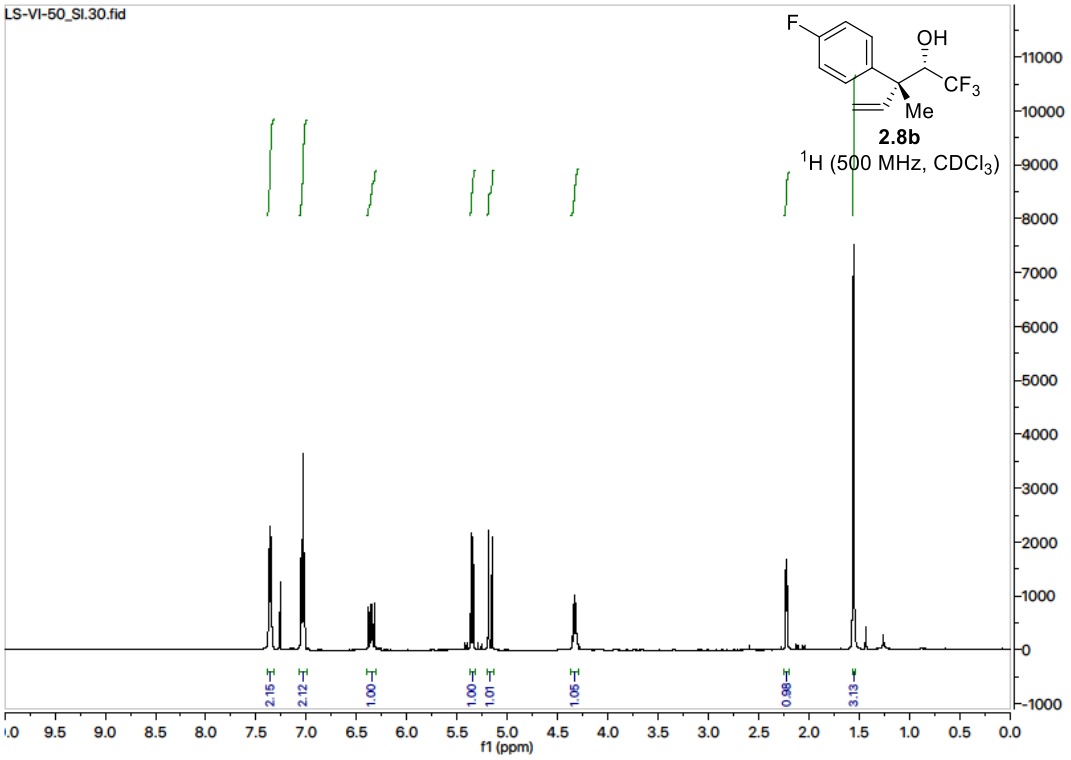
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 7.2 Hz), -116.0 (m).

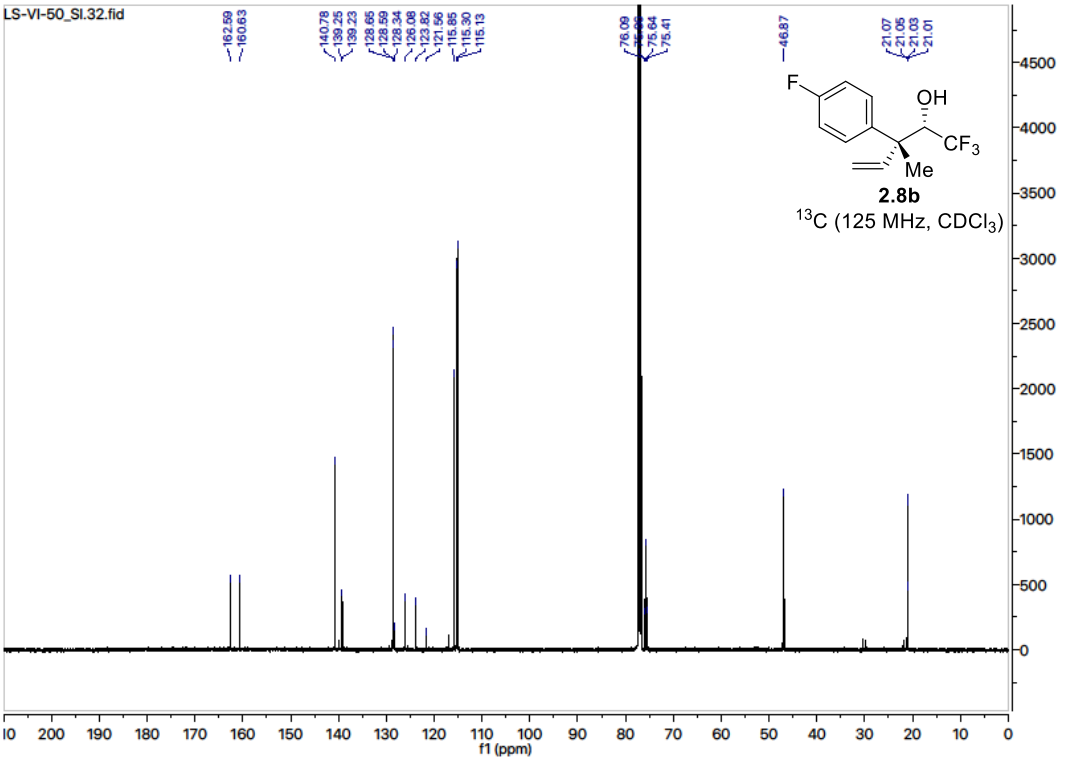
HRMS (CI+, *m/z*) for $C_{12}H_{12}F_4O$: calcd. = 248.0824; found = 248.0821.

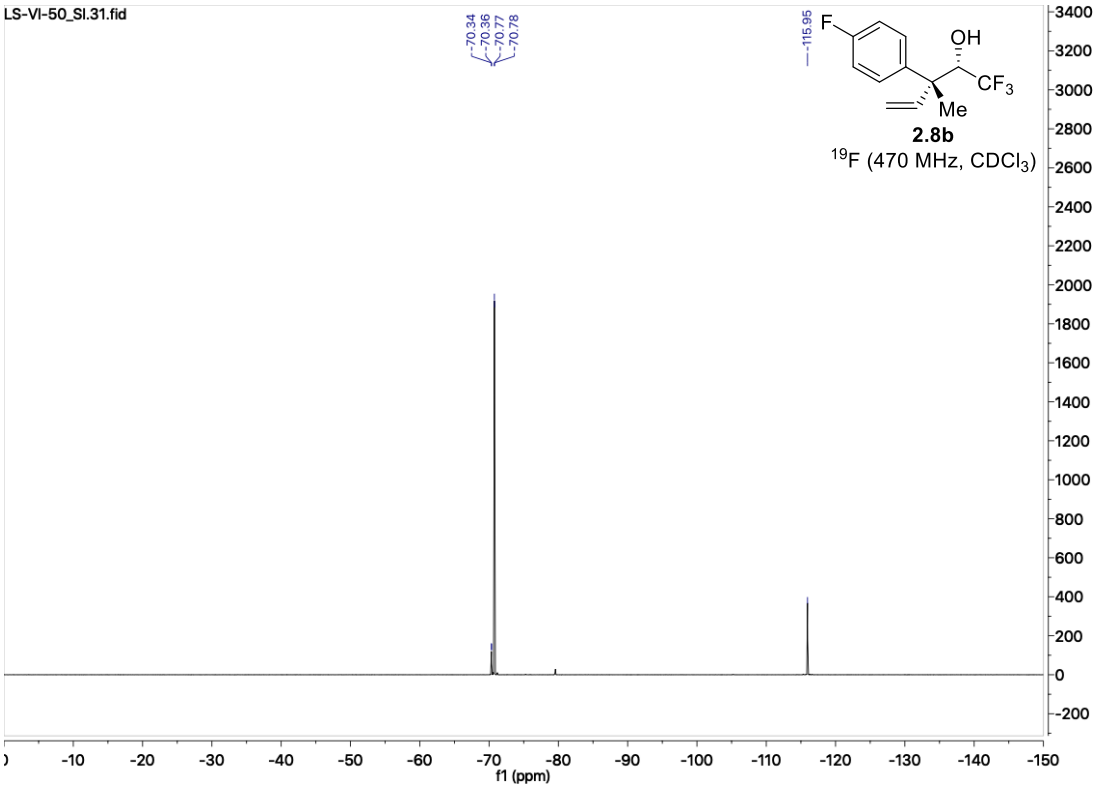
FTIR (neat): 3500, 2950, 2900, 1600, 1500, 1200, 1150, 1100, 900, 800, 600 cm^{-1}.

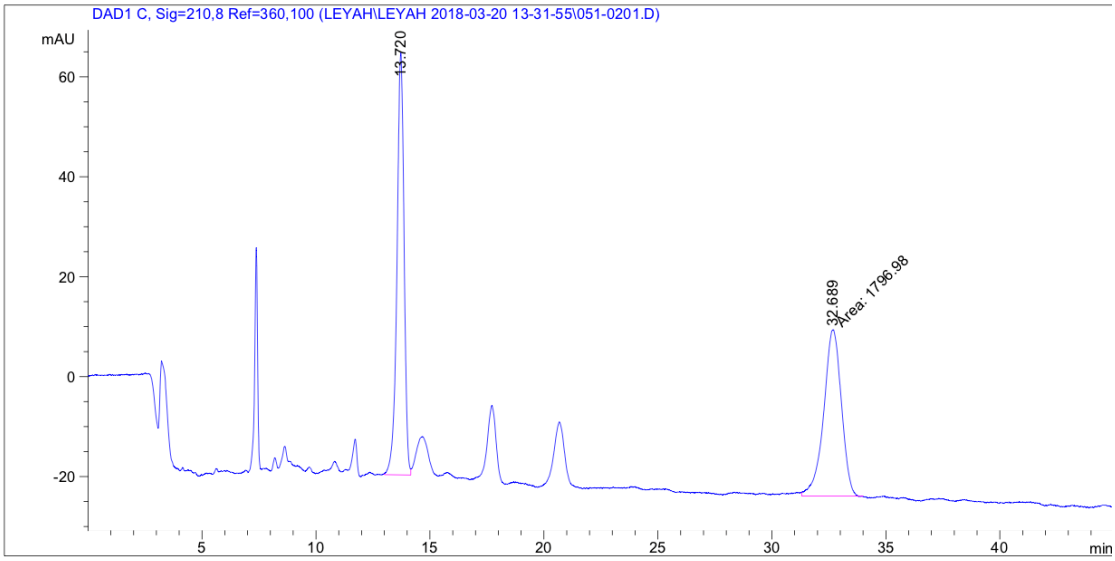
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -15.8 (c = 1.1, $CHCl_3$).

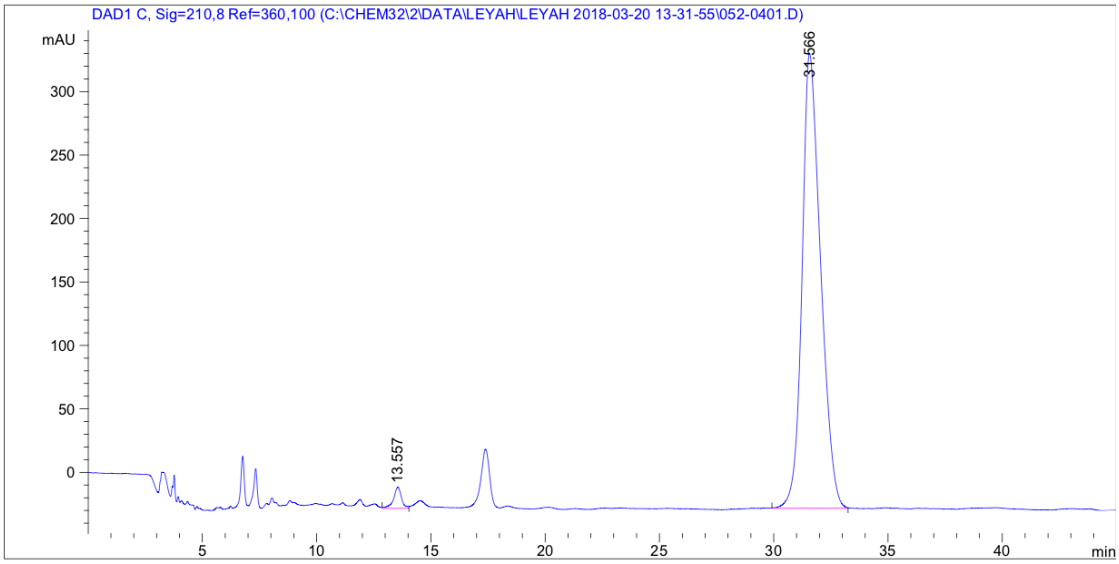

LS-VI-50_SI.30.fid
F
OH
CF3
Me
2.8b
1H (500 MHz, CDCl3)
2.15
2.12
1.00
1.00
1.01
1.06
0.98
3.13
f1 (ppm)


LS-VI-50_SI.32.fid
162.59
160.63
140.78
139.25
139.23
128.65
128.59
128.34
126.08
123.82
121.56
115.85
115.30
115.13
76.09
75.64
75.41
46.87
21.07
21.05
21.03
21.01
F
OH
CF3
Me
2.8b
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-50_SI.31.fid
-70.34
-70.36
-70.77
-70.78
-115.95
F
OH
CF3
Me
2.8b
19F (470 MHz, CDCl3)
f1 (ppm)

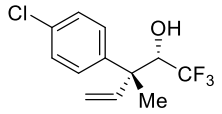


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.720	BV	0.3304	1827.74402	84.47005	50.4244
2	32.689	MM	0.8989	1796.97583	33.31823	49.5756



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.557	VV	0.3532	403.32330	16.61446	1.9546
2	31.566	BB	0.8025	2.02309e4	358.45078	98.0454

(2*S*,3*R*)-1,1,1-trifluoro-3-(4-chlorophenyl)-3-methylpent-4-en-2-ol (2.8c)



2.8c

1,1-Disubstituted allene **2.6c** (65.9 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 5:95 EtOAc/hexanes), the title compound **2.8c** (38.3 mg, 0.14 mmol, 18:1 dr) was obtained as a light yellow oil in 72% yield.

R_f = 0.4 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, 4H), 6.34 (dd, *J* = 10.7, 17.7 Hz, 1H), 5.36 (d, *J* = 10.9 Hz, 1H), 5.17 (d, *J* = 17.6 Hz, 1H), 4.33 (dq, *J* = 7.2, 5.7 Hz, 1H), 2.25 (d, *J* = 5.4 Hz, 1H), 1.55 (q, *J* = 1.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.2, 140.5, 132.9, 128.5, 128.4, 125.0 (q, *J* = 284.0 Hz), 116.1, 75.6 (q, *J* = 28.3 Hz), 47.0, 20.9 (q, *J* = 2.5 Hz).

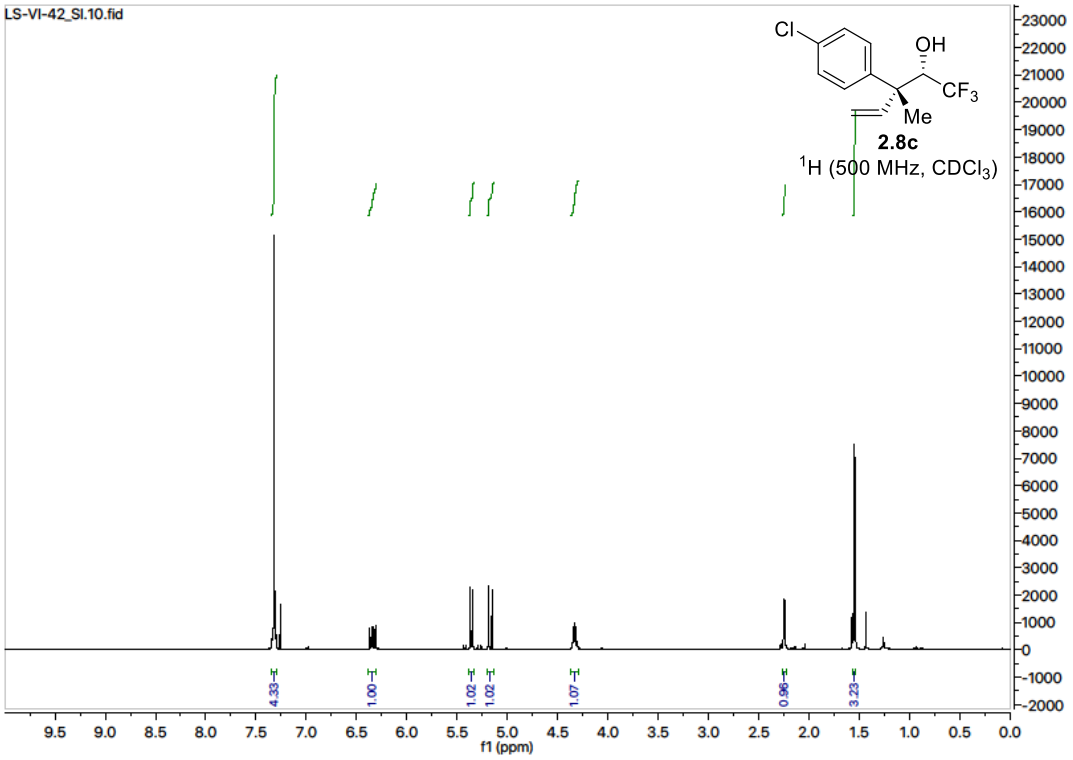
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 7.2 Hz).

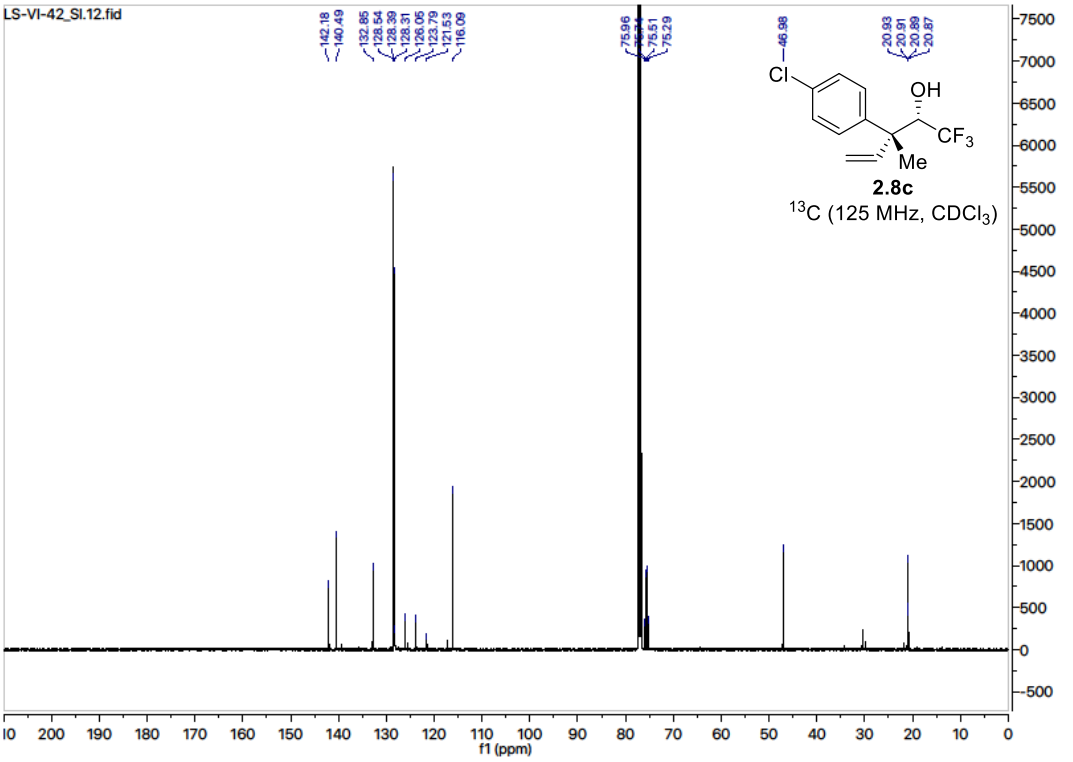
HRMS (CI+, *m/z*) for $C_{12}H_{12}ClF_3O$: calcd. = 264.0529; found = 264.0532.

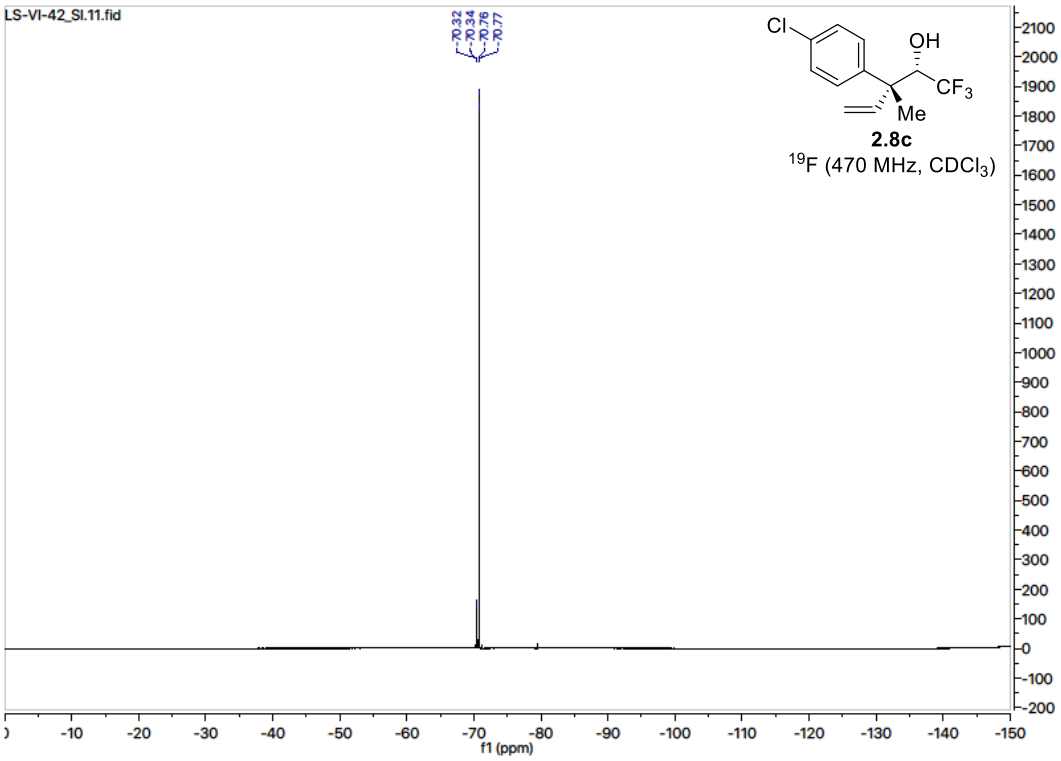
FTIR (neat): 3450, 3000, 1500, 1300, 1150, 1100, 1050, 1000, 900, 800, 350, 300 cm^{-1}.

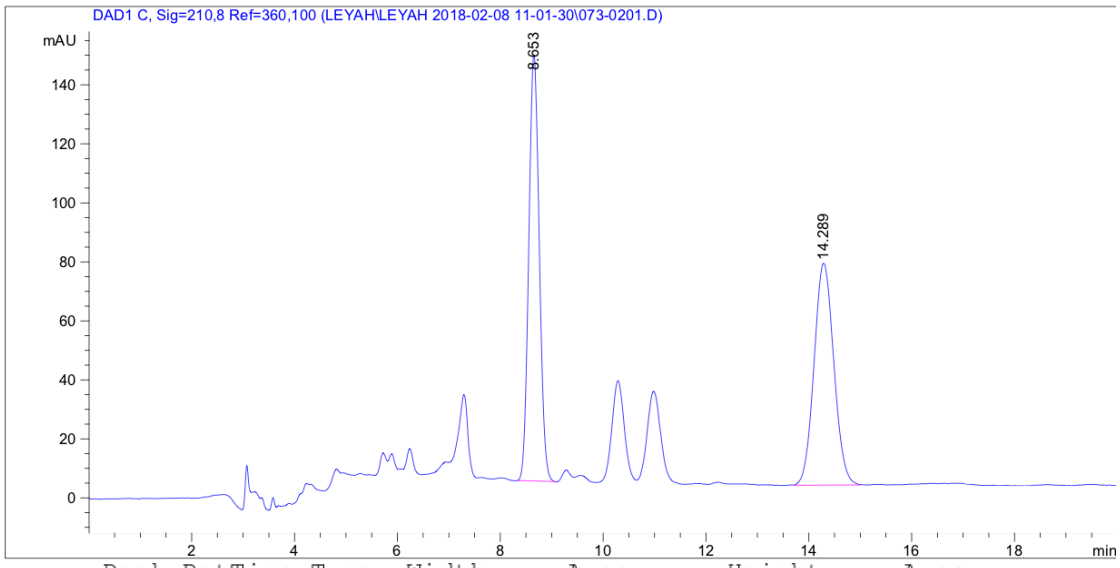
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 93:7, 1.0 mL/min, 210 nm) ee = 96%.

$[\alpha]_D^{24}$= -37.7 (c = 1.1, $CHCl_3$).

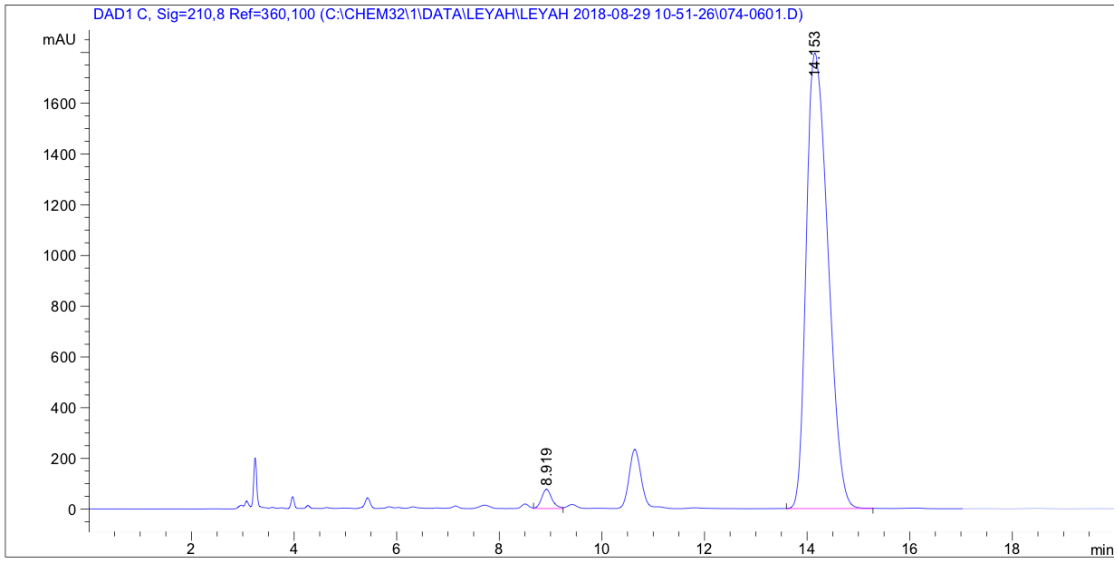

LS-VI-42_SI.10.fid
Cl
OH
CF3
Me
2.8c
1H (500 MHz, CDCl3)
4.33
1.00
1.02
1.02
1.07
0.96
3.23
f1 (ppm)


LS-VI-42_SI.12.fid
142.18
140.49
132.85
128.54
128.39
128.31
126.06
123.79
121.53
116.09
75.96
75.51
75.29
46.98
20.93
20.91
20.89
20.87
Cl
OH
CF3
Me
2.8c
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-42_SI.11.fid
-70.32
-70.34
-70.76
-70.77
Cl
OH
CF3
Me
2.8c
19F (470 MHz, CDCl3)
f1 (ppm)

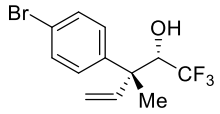


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.653	BB	0.2208	2041.93188	144.58168	50.3916
2	14.289	BB	0.4118	2010.19397	75.20409	49.6084



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.919	VV	0.2118	1052.96545	75.92149	1.9536
2	14.153	BB	0.4694	5.28447e4	1795.55334	98.0464

(2*S*,3*R*)-3-(4-bromophenyl)-1,1,1-trifluoro-3-methylpent-4-en-2-ol (2.8d)



2.8d

1,1-Disubstituted allene **2.6d** (836.4 mg, 4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:9 EtOAc/hexanes), the title compound **2.8d** (528.5 mg, 1.71 mmol, 19:1 dr) was obtained as a light yellow oil in 85% yield.

R_f = 0.4 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 8.9, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.36 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.38 (d, *J* = 10.9 Hz, 1H), 5.19 (d, *J* = 17.5 Hz, 1H), 4.35 (dq, *J* = 7.2, 5.8 Hz, 1H), 2.29 (d, *J* = 5.5 Hz, 1H), 1.56 (q, *J* = 1.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.8, 140.4, 131.5, 128.8, 125.0 (q, *J* = 284.8 Hz), 121.0, 116.1, 75.6 (q, *J* = 28.3 Hz), 47.0, 20.9 (q, *J* = 2.4 Hz).

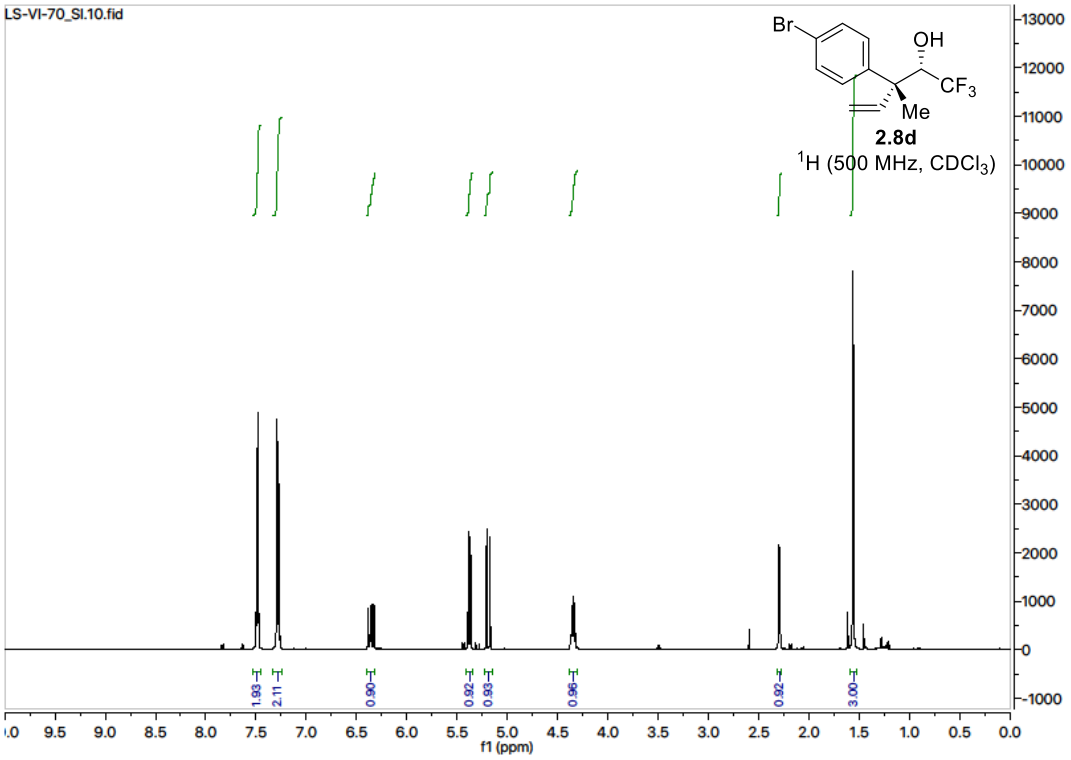
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.75 (d, *J* = 7.2 Hz).

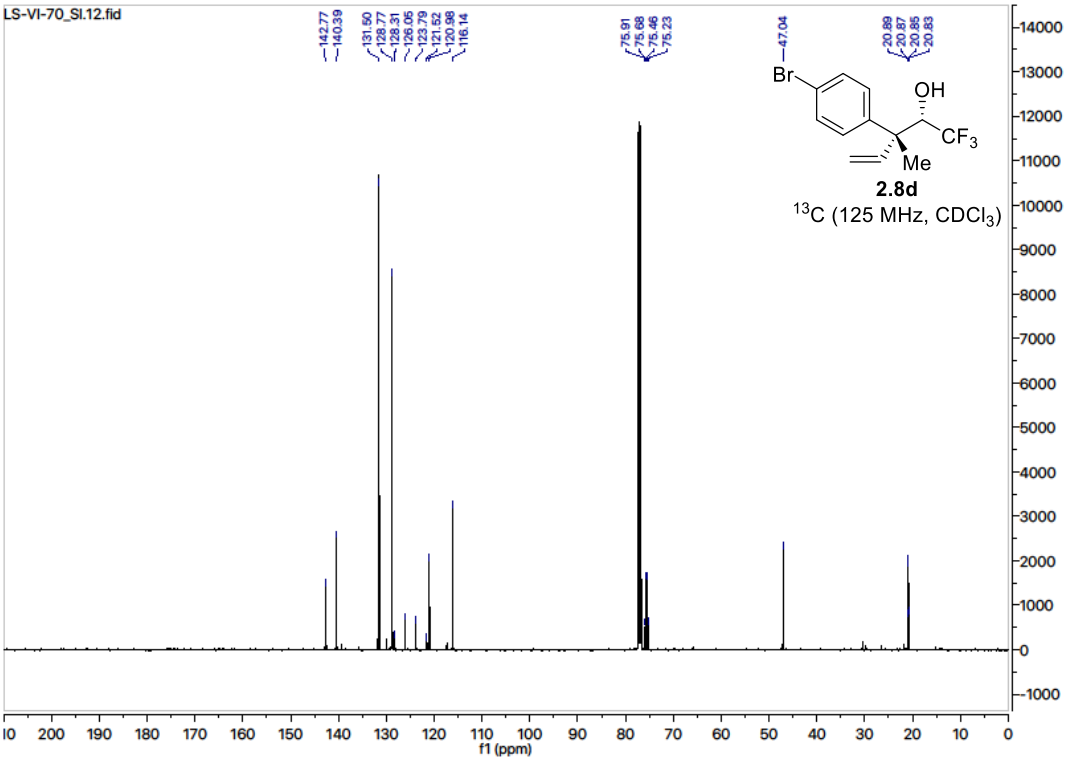
HRMS (CI+, *m/z*) for $C_{12}H_{12}BrF_3O$: calcd. = 308.0024; found = 308.0023.

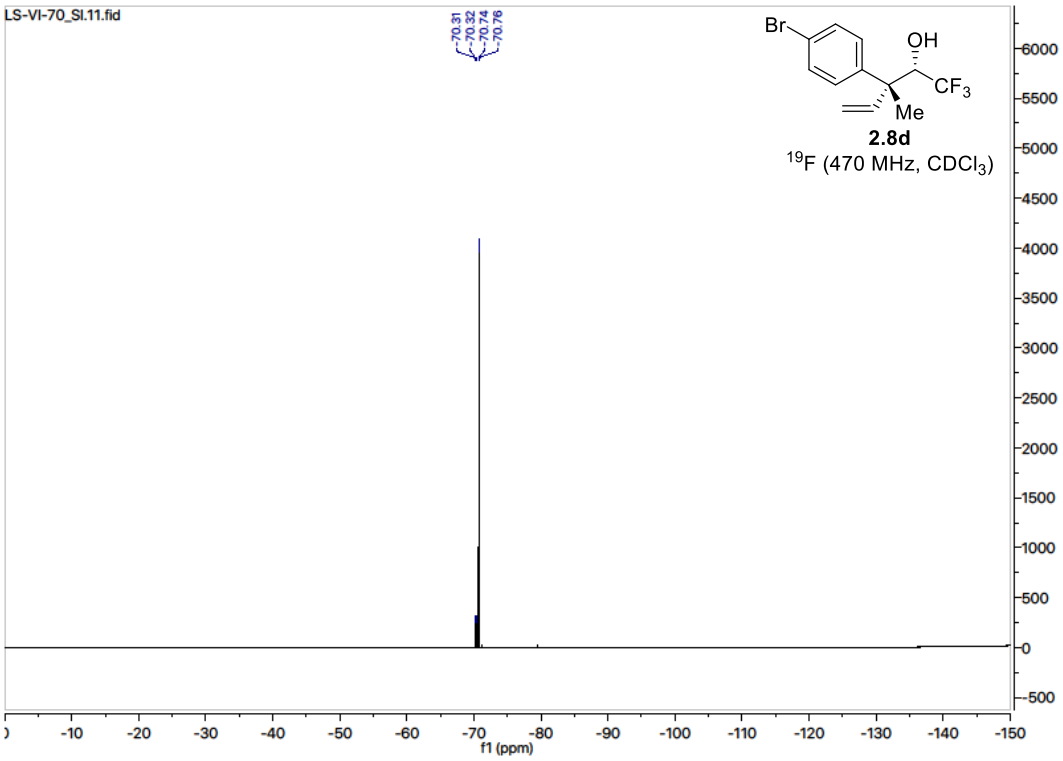
FTIR (neat): 3500, 2950, 1500, 1300, 1150, 110, 1050, 1000, 900, 800, 700, 600 cm^{-1}.

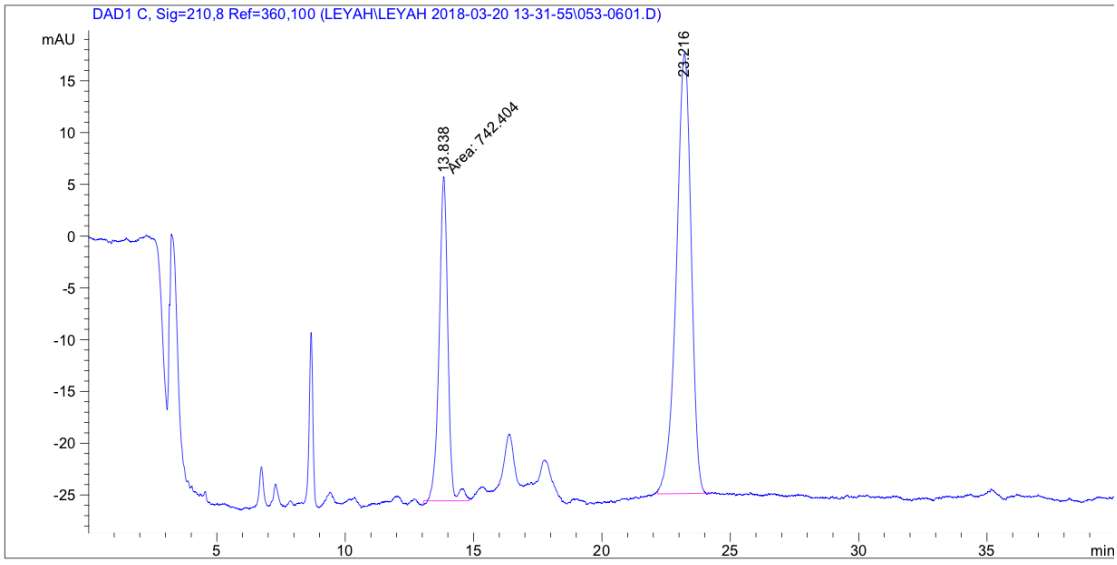
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\alpha]_D^{24}$= -46.4 (c = 1.1, $CHCl_3$).

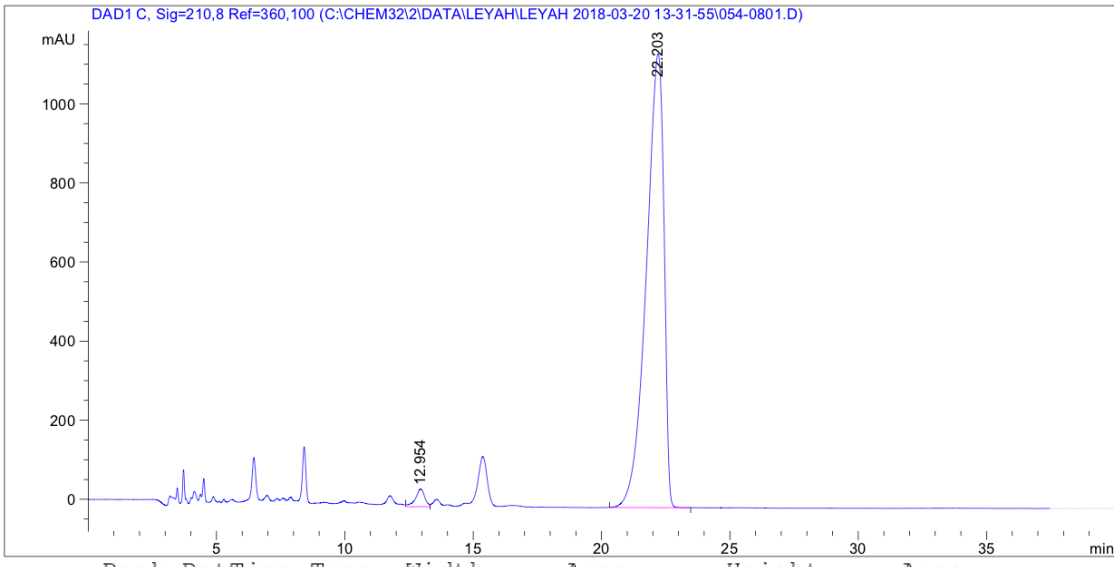

LS-VI-70_SI.10.fid
Br
OH
CF3
Me
2.8d
1H (500 MHz, CDCl3)
1.93
2.11
0.90
0.92
0.93
0.96
0.92
3.00
f1 (ppm)


LS-VI-70_SI.12.fid
142.77
140.39
131.50
128.77
128.31
126.05
123.79
121.52
120.98
116.14
75.91
75.68
75.46
75.23
47.04
20.89
20.87
20.85
20.83
Br
OH
CF3
Me
2.8d
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-70_SI.11.fid
-70.31
-70.32
-70.74
-70.76
Br
OH
CF3
Me
2.8d
19F (470 MHz, CDCl3)
f1 (ppm)

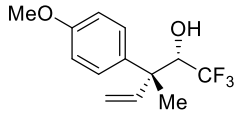


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.838	MM	0.3950	742.40375	31.32551	30.3754
2	23.216	BB	0.5790	1701.69189	42.50950	69.6246



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.954	VV	0.3776	1122.12097	44.59044	2.0074
2	22.203	BB	0.7326	5.47777e4	1148.14624	97.9926

(2*S*,3*R*)-1,1,1-trifluoro-3-(4-methoxyphenyl)-3-methylpent-4-en-2-ol (2.8e)



2.8e

1,1-Disubstituted allene **2.6e** (64.9 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 5:95 EtOAc/hexanes), the title compound **2.8e** (39.6 mg, 0.16 mmol, 14:1 dr) was obtained as a light yellow oil in 79% yield.

R_f = 0.3 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.3 (m, 2H), 6.88 (m, 2H), 6.37 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.34 (d, *J* = 11.0 Hz, 1H), 5.17 (d, *J* = 17.7 Hz, 1H), 4.32 (dq, *J* = 5.4, 1.9 Hz, 1H), 3.80 (s, 3H), 2.17 (d, *J* = 5.1 Hz, 1H), 1.54 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.4, 140.9, 135.4, 128.0, 125.1 (q, *J* = 282.9 Hz), 115.4, 113.8, 75.9 (q, *J* = 27.9 Hz), 55.3, 46.7, 21.1 (q, *J* = 2.4Hz).

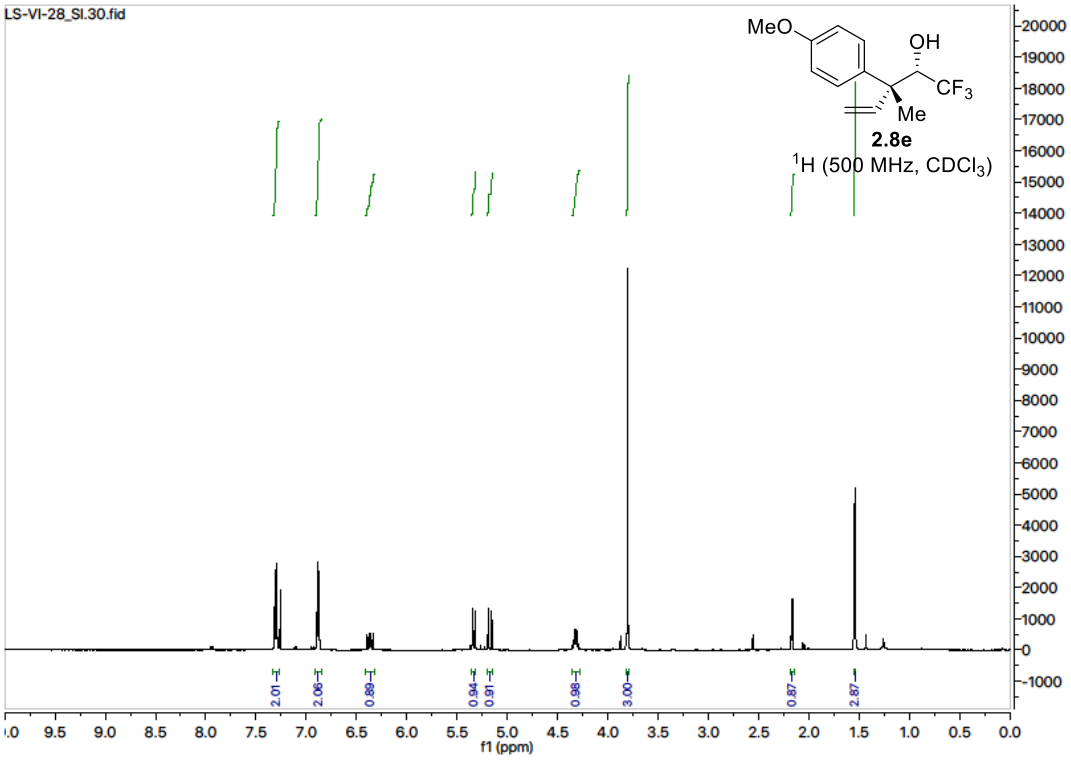
^{19}F NMR (470 MHz, $CDCl_3$) δ:-70.7 (d, *J* = 7.2 Hz).

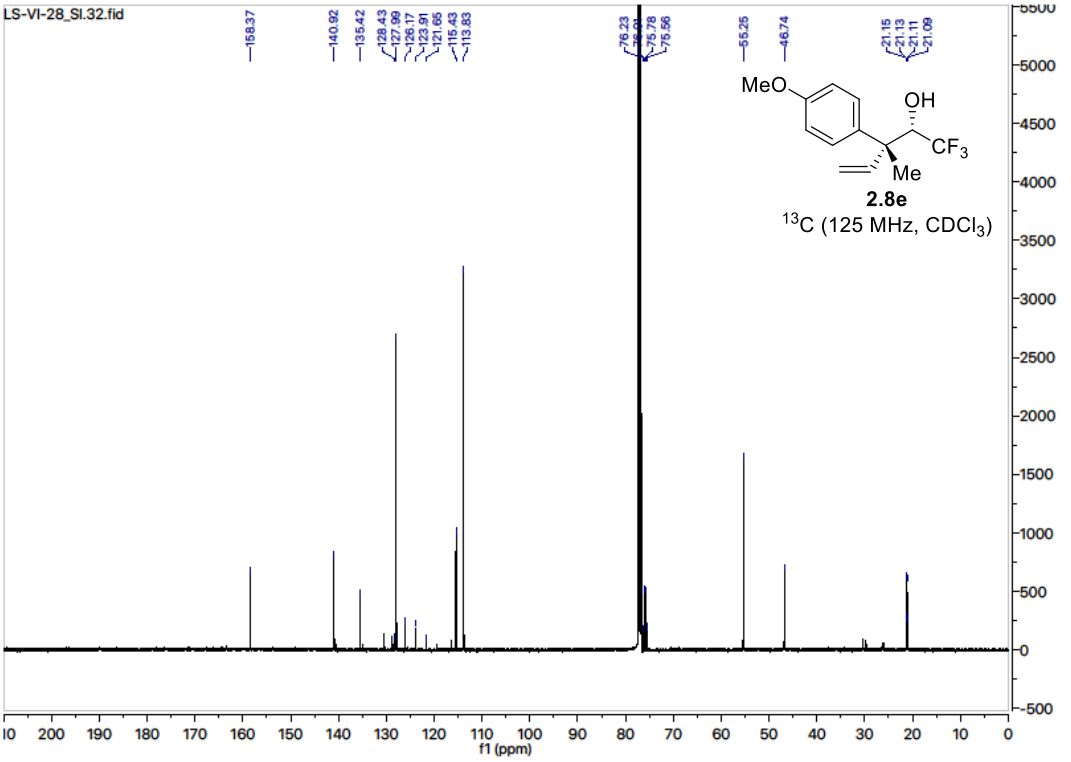
HRMS (APPI, *m/z*) for $C_{13}H_{15}F_3O_2$: calcd. = 261.1097; found = 261.1096.

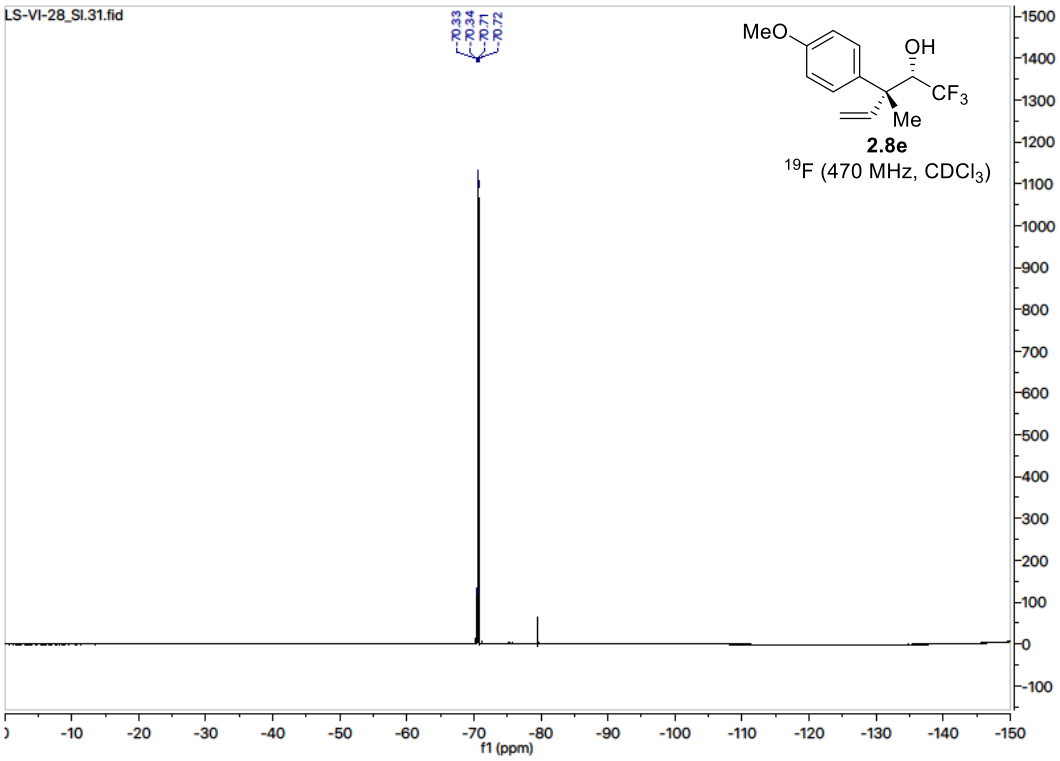
FTIR (neat): 3500, 2950, 2800, 1510, 1250, 1150, 1050, 1000, 900, 800 cm^{-1}.

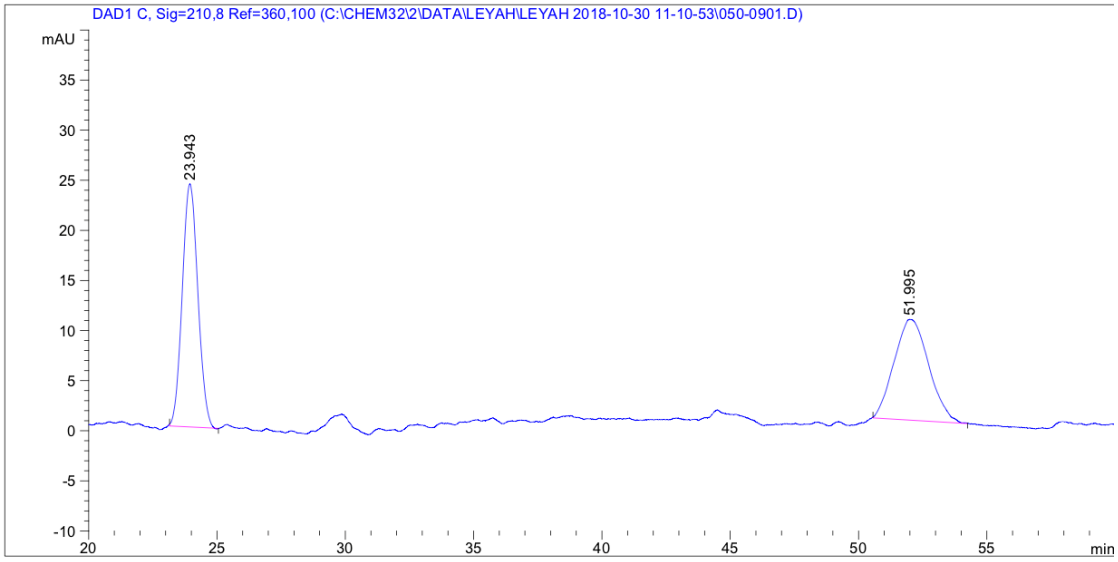
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 92:8, 1.0 mL/min, 210 nm) ee = 96%.

$[\alpha]_D^{24}$ = -22.8 (c = 1.1, $CHCl_3$).

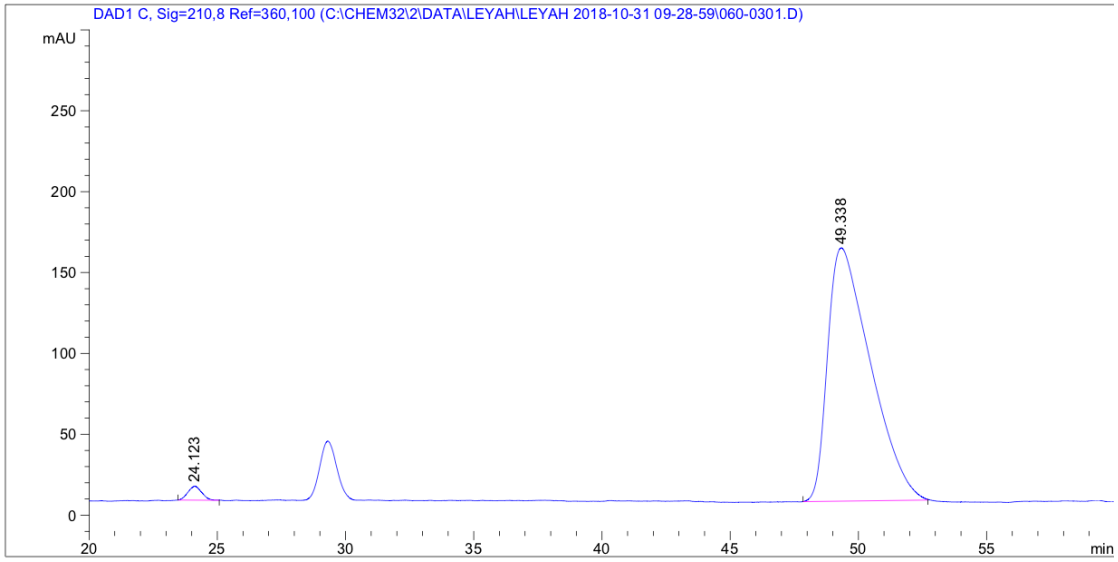

LS-VI-28_SI.30.fid
MeO
OH
CF3
Me
2.8e
1H (500 MHz, CDCl3)
2.01
2.06
0.89
0.94
0.91
0.98
3.00
0.87
2.87
f1 (ppm)


LS-VI-28_SI.32.fid
158.37
140.92
135.42
128.43
127.99
126.17
123.91
121.65
115.43
113.83
76.23
75.78
75.56
55.25
46.74
21.15
21.13
21.11
21.09
MeO
OH
CF3
Me
2.8e
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-28_SI.31.fid
-70.33
-70.34
-70.71
-70.72
MeO
OH
CF3
Me
2.8e
19F (470 MHz, CDCl3)
f1 (ppm)

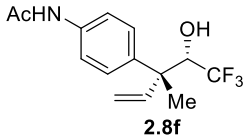


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.943	BB	0.6220	1023.28094	24.26306	52.0288
2	51.995	BB	1.1013	943.47607	10.04927	47.9712



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.123	BB	0.5034	322.22144	8.59505	1.7409
2	49.338	BB	1.6031	1.81863e4	156.57919	98.2591

***N*-(4-((3*R*,4*S*)-5,5,5-trifluoro-4-hydroxy-3-methylpent-1-en-3-yl)phenyl)acetamide (2.8f)**



2.8f

1,1-Disubstituted allene **2.6f** (74.9 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:1 EtOAc/hexanes), the title compound **2.8f** (36.7 mg, 0.13 mmol, 11:1 dr) was obtained as a light yellow oil in 64% yield.

R_f = 0.2 (10:1 CH_2Cl_2 : MeOH)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.37 (dd, *J* = 11.0, 17.6 Hz, 1H), 5.32 (d, *J* = 10.9 Hz, 1H), 5.16 (d, *J* = 17.7 Hz, 1H), 4.32 (dq, *J* = 5.2, 2.0 Hz, 1H), 3.04 (d, *J* = 5.6 Hz, 1H), 2.11 (s, 3H), 1.52 (bs, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.9, 140.7, 140.1, 136.4, 127.5, 125.2 (q, *J* = 284.3 Hz), 119.9, 115.5, 75.6 (q, *J* = 28.2 Hz), 47.0, 24.4, 21.1 (q, *J* = 1.9 Hz).

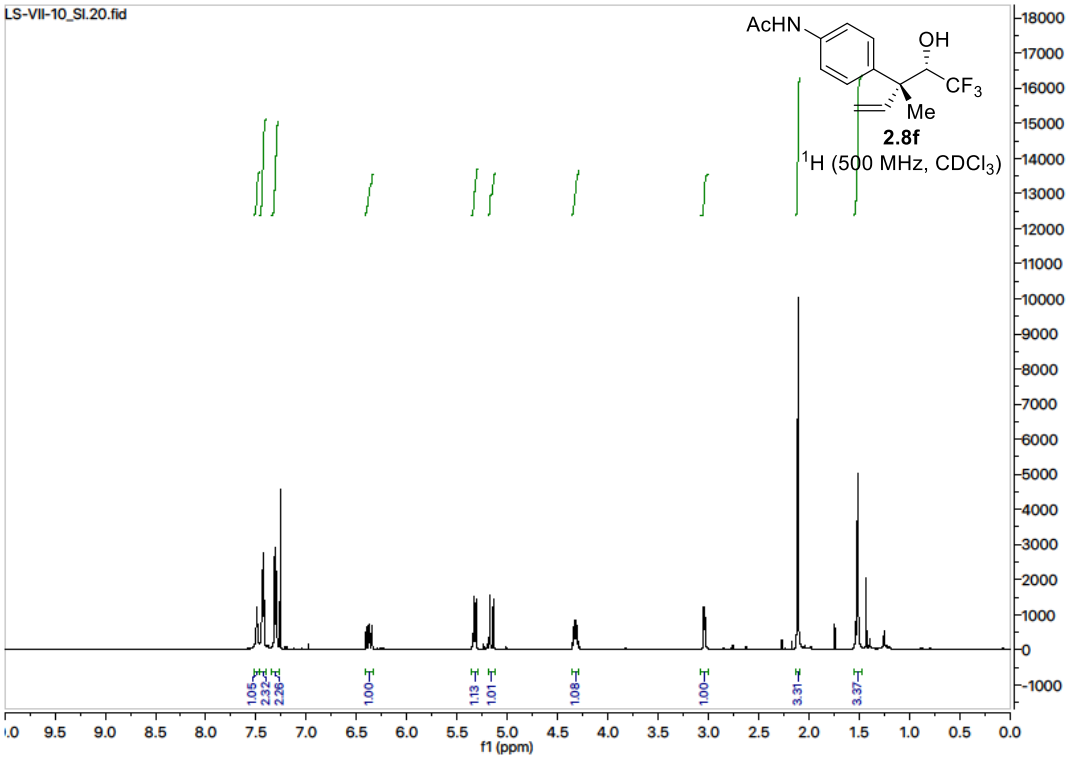
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.7 (d, *J* = 7.1 Hz).

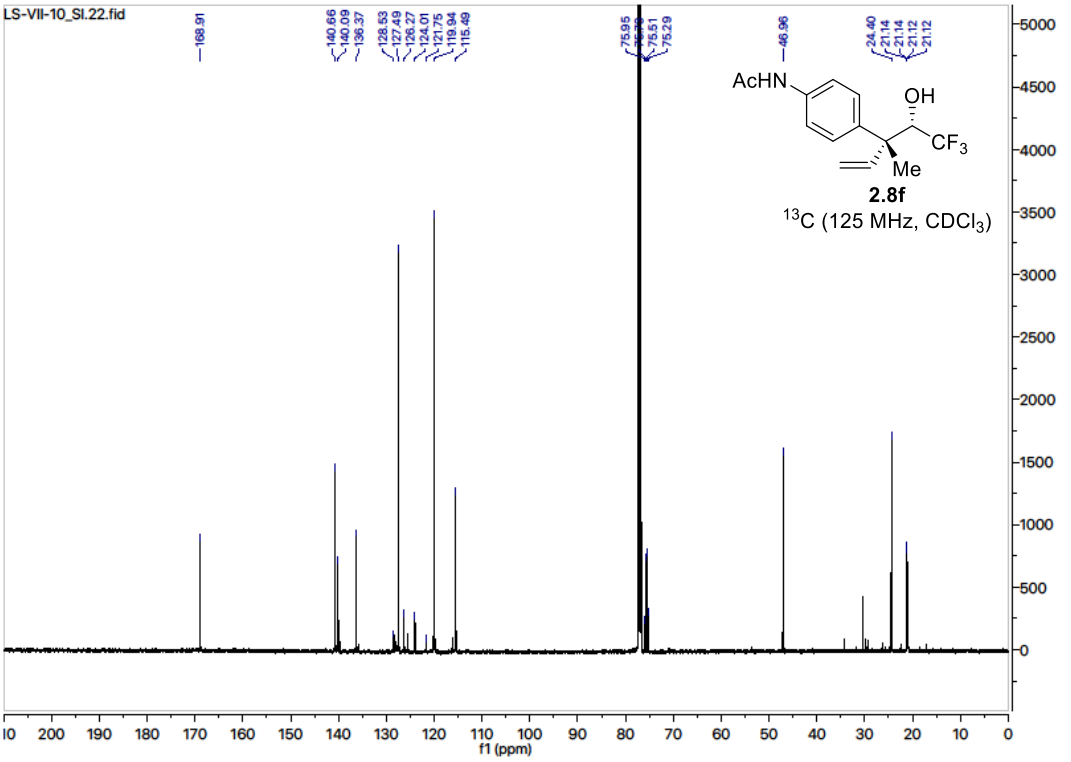
HRMS (ESI+H, *m/z*) for $C_{14}H_{16}F_3NO_2$: calcd. = 288.1206; found = 288.1211.

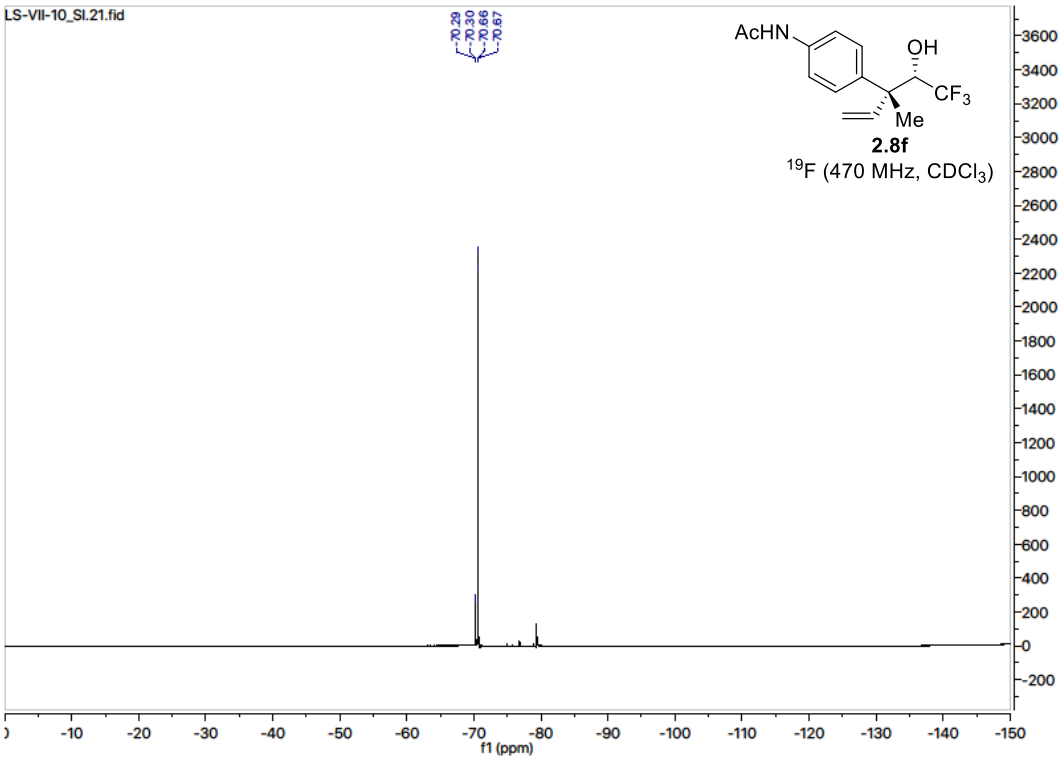
FTIR (neat): 3300, 2300, 1700, 1600, 1500, 1350, 1250, 1150, 1100, 650 cm^{-1}.

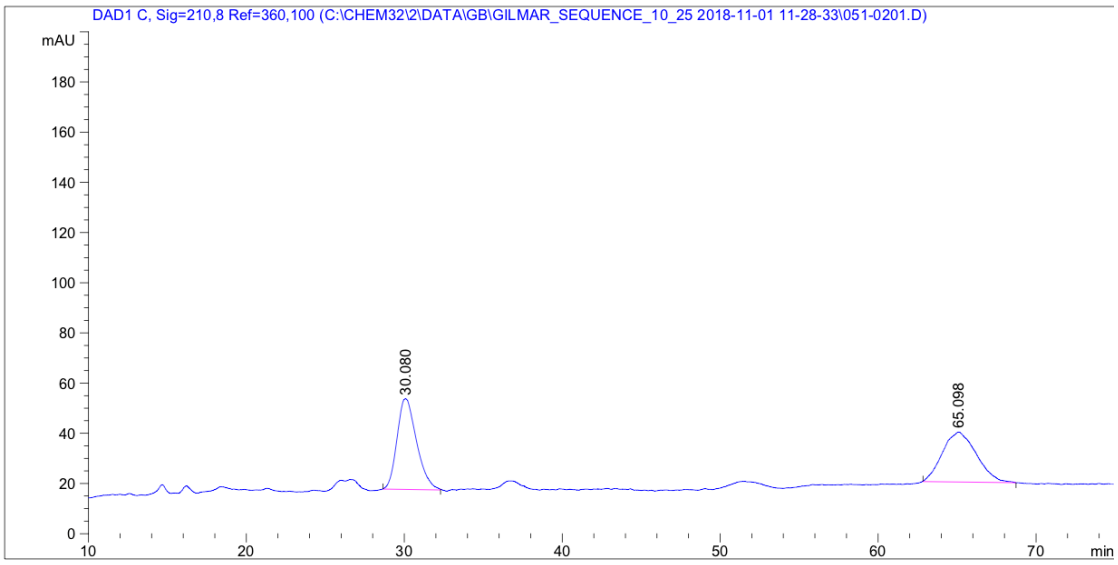
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 90:10, 1.0 mL/min, 210 nm) ee = 90%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -29.5 (c = 1.1, $CHCl_3$).

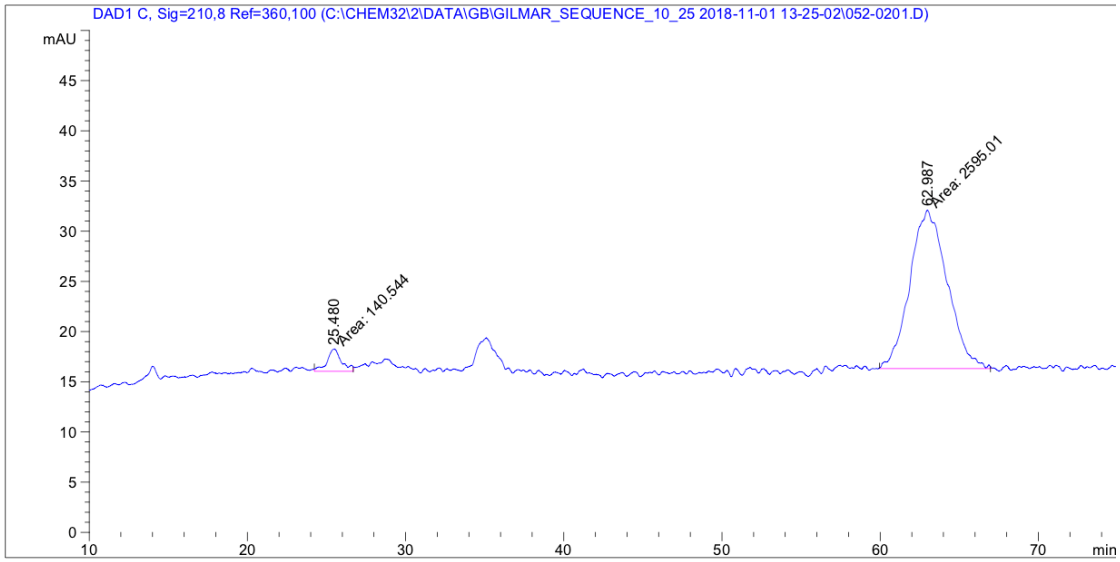

LS-VII-10_SI.20.fid
AcHN
OH
CF3
Me
2.8f
1H (500 MHz, CDCl3)
f1 (ppm)


LS-VII-10_SI.22.fid
AcHN
OH
CF3
Me
2.8f
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VII-10_SI.21.fid
-70.29
-70.30
-70.66
-70.67
AcHN
OH
CF3
Me
2.8f
19F (470 MHz, CDCl3)
f1 (ppm)

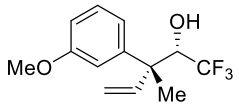


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.080	BB	1.0321	3108.08911	36.11449	51.0859
2	65.098	BB	1.7562	2975.96167	19.88336	48.9141



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.480	MM	1.0401	140.54420	2.25214	5.1377
2	62.987	MM	2.7422	2595.00830	15.77224	94.8623

(2*S*,3*R*)-1,1,1-trifluoro-3-(3-methoxyphenyl)-3-methylpent-4-en-2-ol (2.8g)



2.8g

1,1-Disubstituted allene **2.6g** (64.1 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:10 EtOAc/hexanes), the title compound **2.8g** (39.6 mg, 0.15 mmol, 18:1 dr) was obtained as a light yellow oil in 76% yield.

R_f = 0.3 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (t, *J* = 8.0 Hz, 1H), 6.98 (m, 1H), 6.94 (m, 1H), 6.80 (m, 1H), 6.38 (dd, *J* = 11.1, 17.7 Hz, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 17.7 Hz, 1H), 4.37 (dq, *J* = 5.3, 2.0 Hz, 1H), 3.81 (s, 3H), 2.21 (d, *J* = 5.1 Hz, 1H), 1.55 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.7, 145.5, 140.3, 129.5, 125.0 (q, *J* = 283.8 Hz), 119.0, 115.8, 113.7, 111.5, 75.9 (q, *J* = 28.3 Hz), 55.2, 47.4, 21.0 (q, *J* = 2.6 Hz).

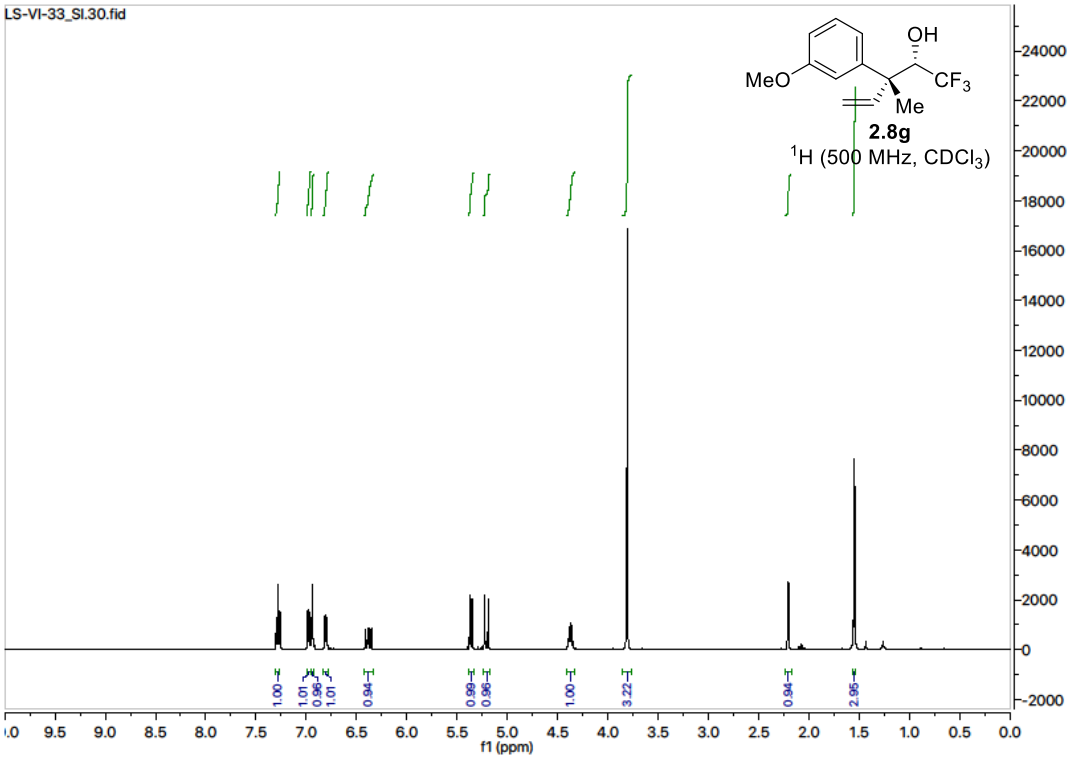
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.7 (d, *J* = 7.2 Hz).

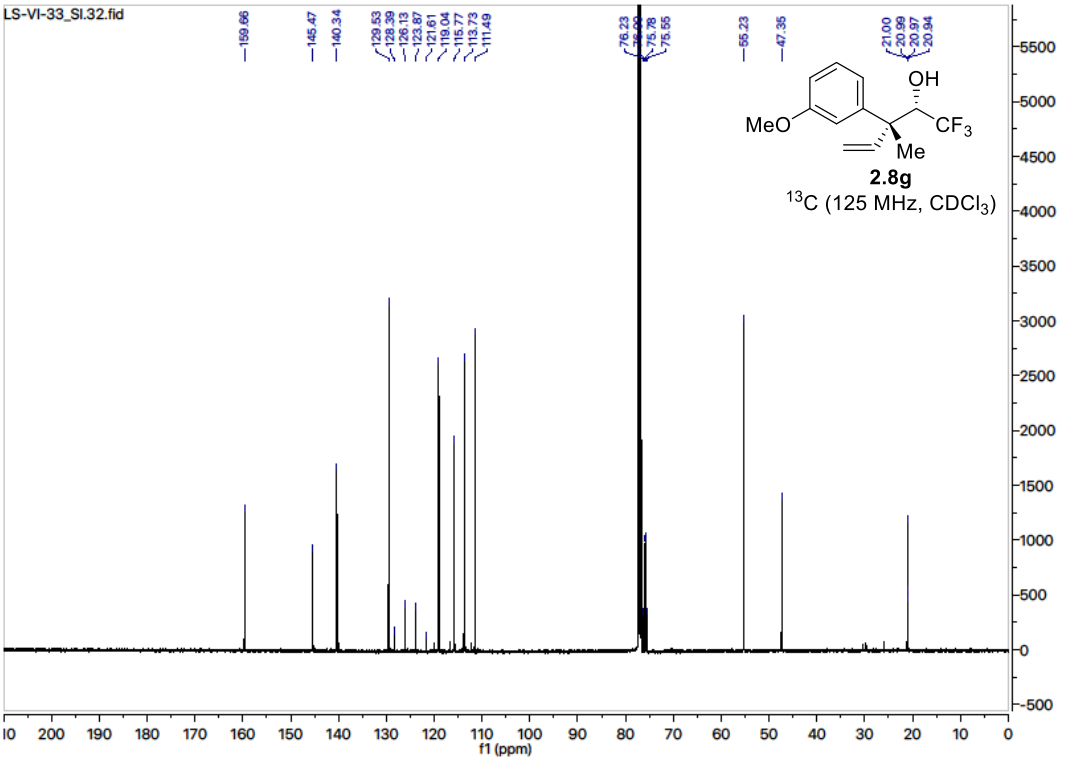
HRMS (APPI, *m/z*) for $C_{13}H_{15}F_3O_2$: calcd. = 261.1097; found = 261.1091.

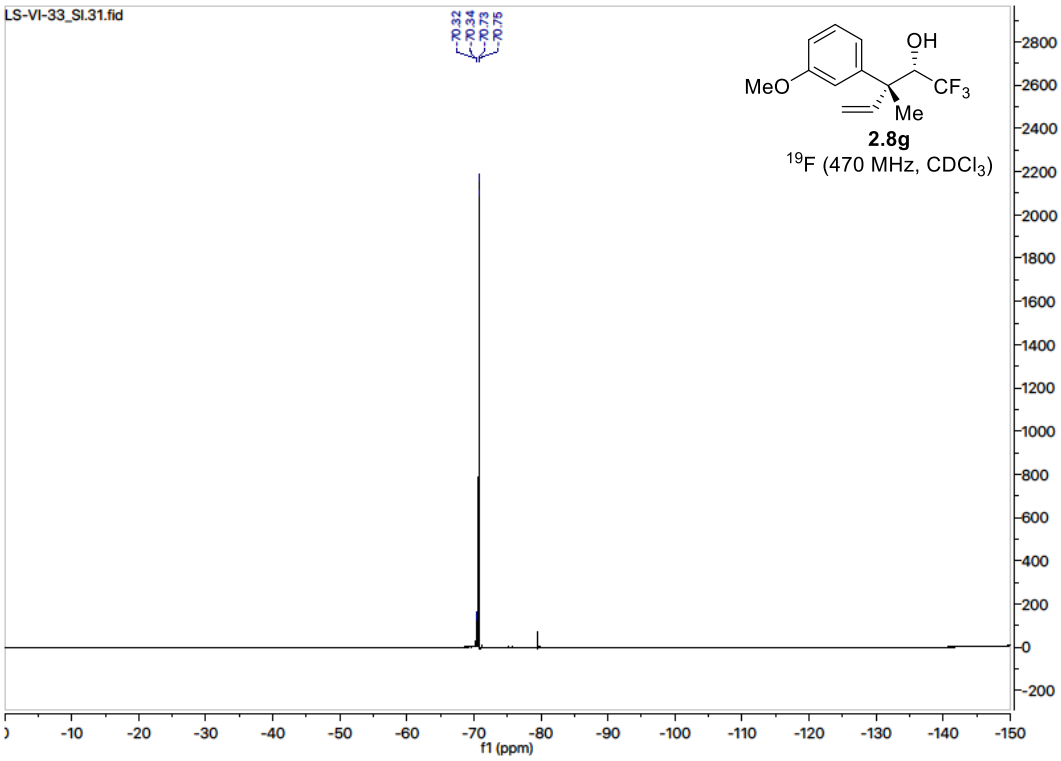
FTIR (neat): 3450, 3000, 2850, 1550, 1450, 1250, 1150, 1100, 1000, 900, 800, 700 cm^{-1}.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -28.0 (c = 1.1, $CHCl_3$).


LS-VI-33_SI.30.fid
OH
MeO
CF3
Me
2.8g
1H (500 MHz, CDCl3)
f1 (ppm)


LS-VI-33_SI.32.fid
159.66
145.47
140.34
129.53
128.39
126.13
123.87
121.61
119.04
115.77
113.73
111.49
76.23
75.78
75.55
55.23
47.35
21.00
20.99
20.97
20.94
OH
MeO
CF3
Me
2.8g
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-33_SI.31.fid
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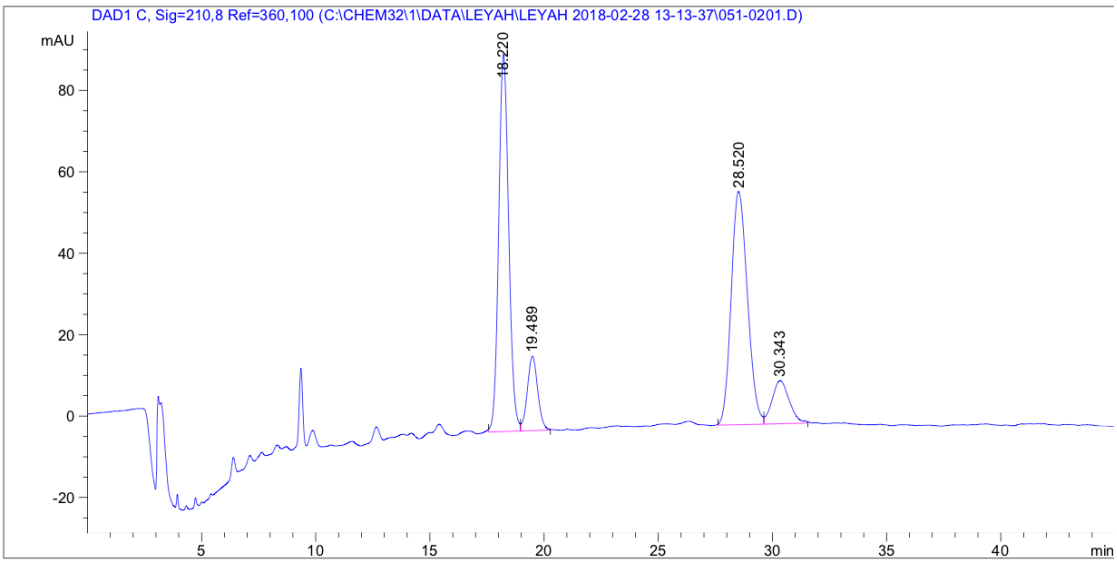
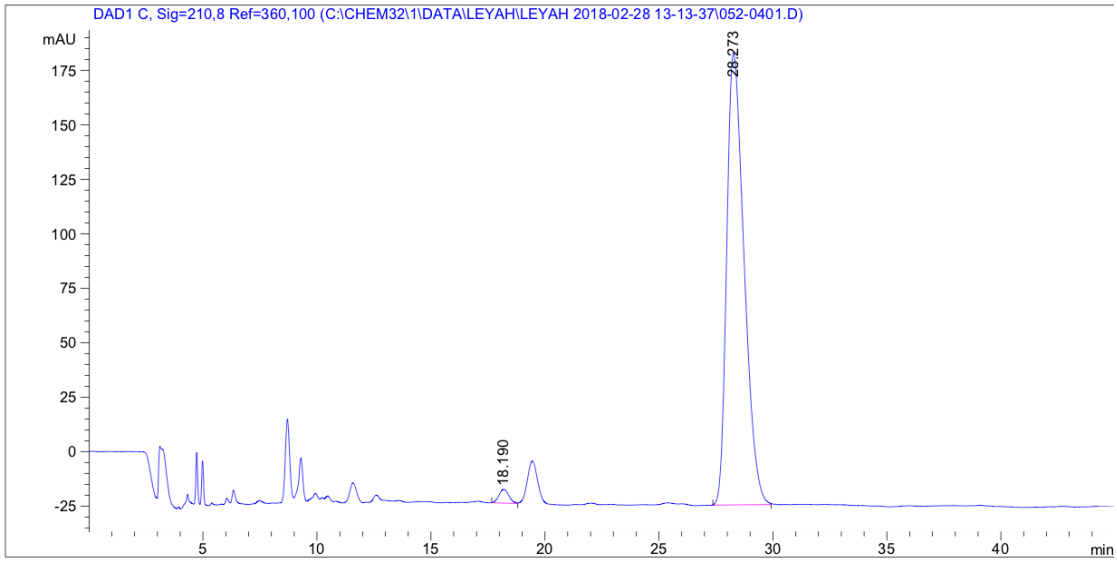
-70.34
-70.73
-70.75
OH
MeO
CF3
Me
2.8g
19F (470 MHz, CDCl3)
f1 (ppm)

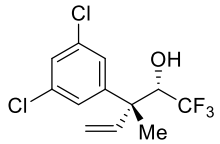


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.220	BV	0.4709	2818.31250	92.65637	41.5135
2	19.489	VB	0.4854	580.21588	18.32599	8.5465
3	28.520	BV	0.7660	2837.34351	57.27100	41.7938
4	30.343	VB	0.7253	553.03925	10.58979	8.1462



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.190	BV	0.4759	191.25313	6.30483	1.7138
2	28.273	BB	0.8151	1.09685e4	207.37895	98.2862

(2*S*,3*R*)-3-(3,5-dichlorophenyl)-1,1,1-trifluoro-3-methylpent-4-en-2-ol (2.8h)



2.8h

1,1-Disubstituted allene **2.6h** (80 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 4:96 EtOAc/hexanes), the title compound **2.8h** (42.5 mg, 0.14 mmol, 19:1 dr) was obtained as a yellow oil in 71% yield.

R_f = 0.38 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26 (s, 3H), 6.31 (dd, *J* = 9.7, 15.4 Hz, 1H), 5.41 (d, *J* = 9.7 Hz, 1H), 5.20 (d, *J* = 15.4 Hz, 1H), 4.30 (dq, *J* = 6.3 Hz, 1H), 2.30 (d, *J* = 6.3 Hz, 1H, O*H*), 1.53 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.6, 139.4, 135.0, 127.1, 125.8, 124.9 (q, *J* = 285 Hz), 116.8, 75.4 (q, *J* = 30 Hz), 47.2, 21.0.

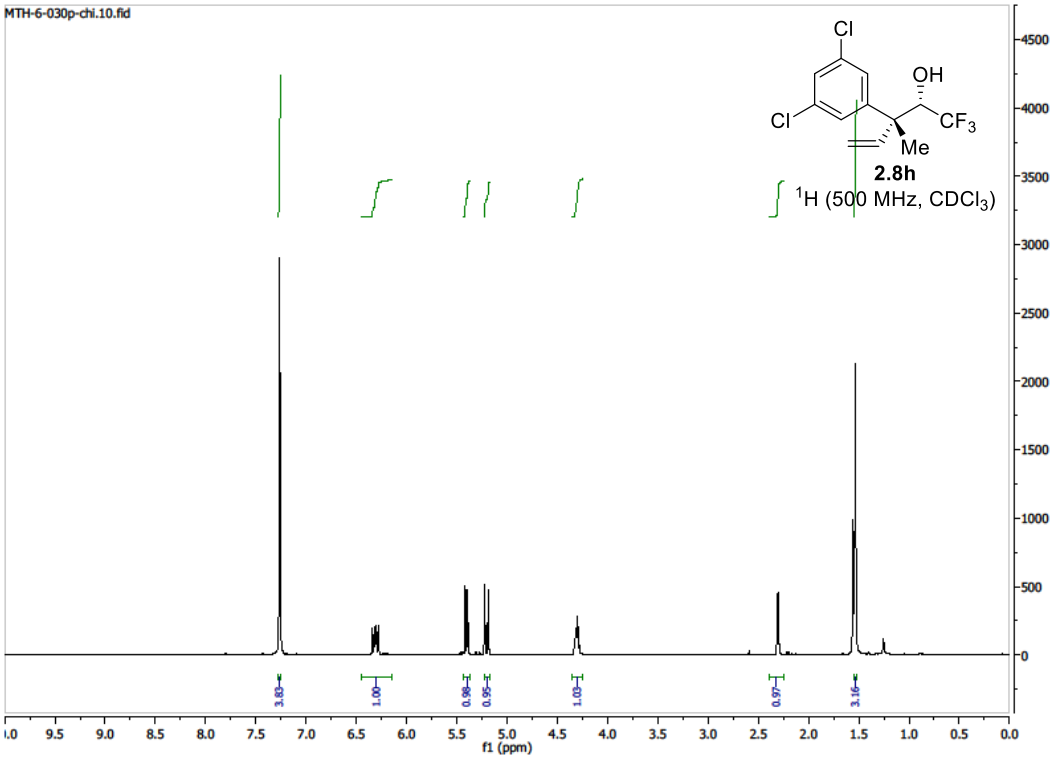
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.9 (d, *J* = 6.3 Hz).

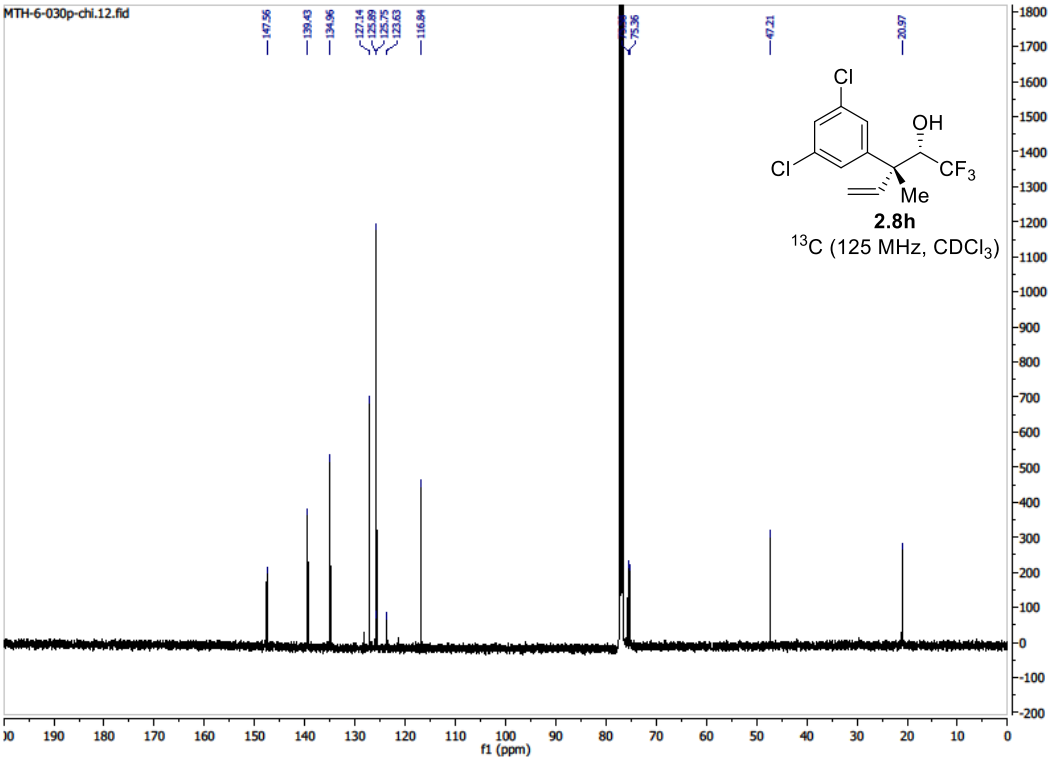
HRMS (Cl+, *m/z*) for $C_{12}H_{11}F_3Cl_2$: calcd. = 298.0139; found = 298.0136.

FTIR (neat): 3442, 2981, 1586, 1564, 1417, 1271, 1165, 1131, 1033, 932, 801, 699 cm^{-1}.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 99:1, 1.0 mL/min, 210 nm) ee = 95%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -31.3 (c = 1.0, $CHCl_3$).


MTH-6-030p-chi.10.fid
Cl
OH
Cl
CF3
Me
2.8h
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-030p-chi.12.fid
147.56
139.43
134.96
127.14
125.89
125.75
123.63
116.84
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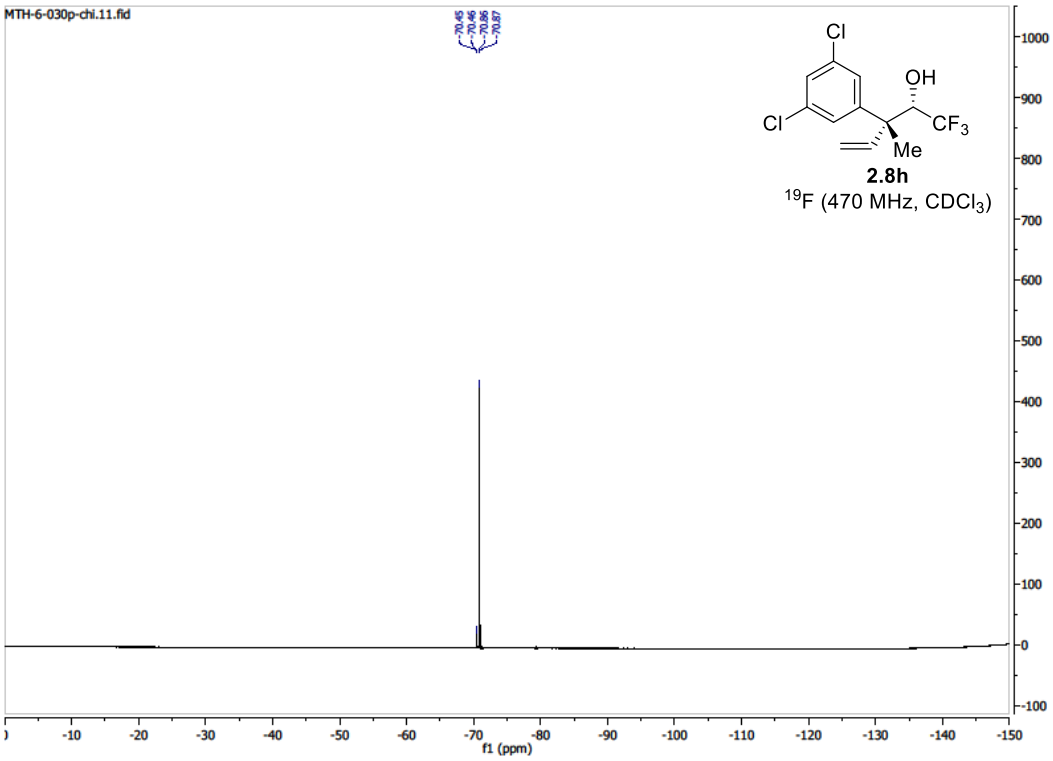
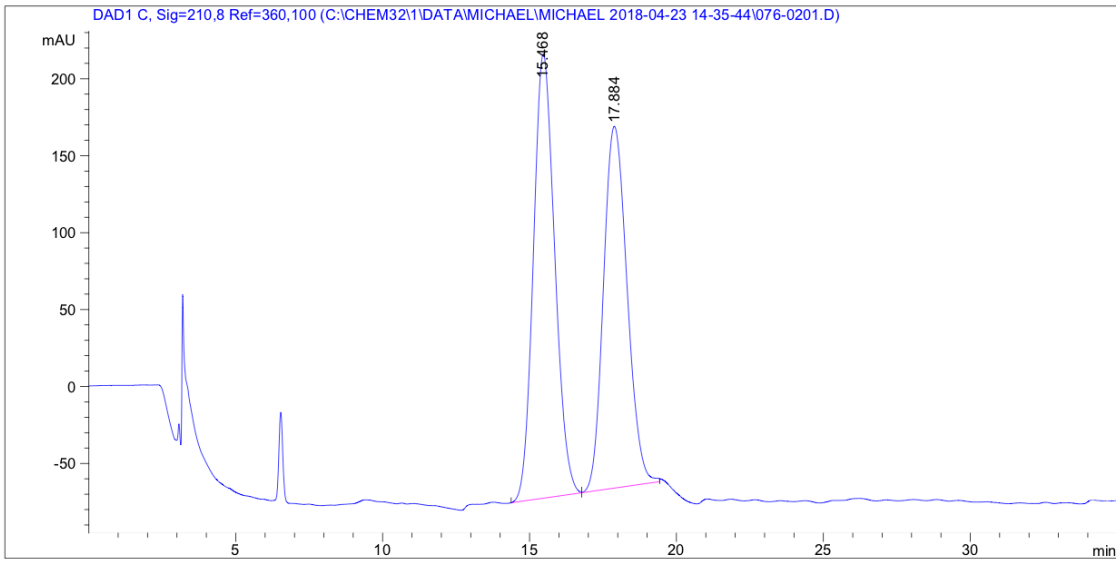
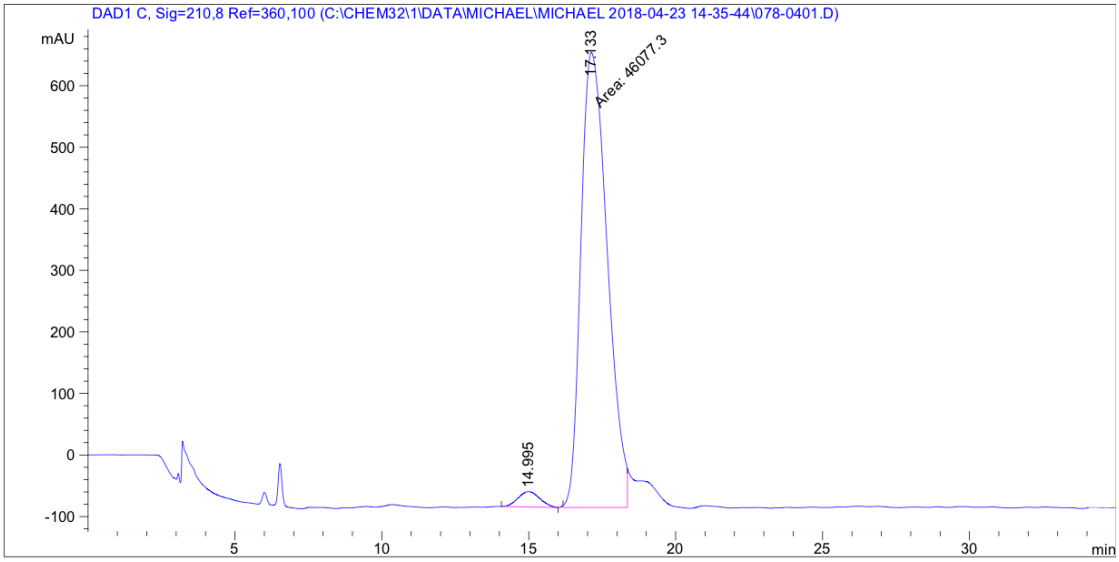
20.97
Cl
OH
Cl
CF3
Me
2.8h
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-030p-chi.11.fid
Cl
OH
Cl
CF3
Me
2.8h
19F (470 MHz, CDCl3)
f1 (ppm)

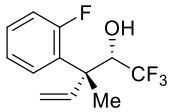


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.468	BV	0.7719	1.45451e4	288.63223	52.5736
2	17.884	VB	0.8752	1.31211e4	235.07341	47.4264



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.995	BV	0.7664	1270.97290	24.86094	2.6843
2	17.133	MF	1.0388	4.60773e4	739.29962	97.3157

(2*S*,3*R*)-1,1,1-trifluoro-3-(2-fluorophenyl)-3-methylpent-4-en-2-ol (2.8i)



2.8i

1,1-Disubstituted allene **2.6i** (59.2 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 4:96 EtOAc/hexanes), the title compound **2.8i** (28.8 mg, 0.12 mmol, 13:1) was obtained as a yellow oil in 58% yield.

R_f = 0.39 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (t, *J* = 10 Hz, 1H), 7.27 (m, 1H), 7.13 (t, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 8.7, 10.0 Hz, 1H), 6.45 (dd, *J* = 9.9, 17.6 Hz, 1H), 5.30 (d, *J* = 9.9 Hz, 1H), 5.13 (d, *J* = 17.6 Hz, 1H), 4.81 (dq, *J* = 6.6 Hz, 1H), 2.32 (d, *J* = 6.6 Hz, 1H, O*H*), 1.62 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.9 (d, *J* = 242 Hz), 140.3, 130.1 (d, *J* = 12 Hz), 129.1 (d, *J* = 9 Hz), 128.9 (d, *J* = 5 Hz), 125.1 (q, *J* = 285 Hz), 124.3 (d, *J* = 3 Hz), 116.3 (d, *J* = 24 Hz), 115.5, 72.9 (dq, *J* = 8, 28 Hz), 46.8, 18.4.

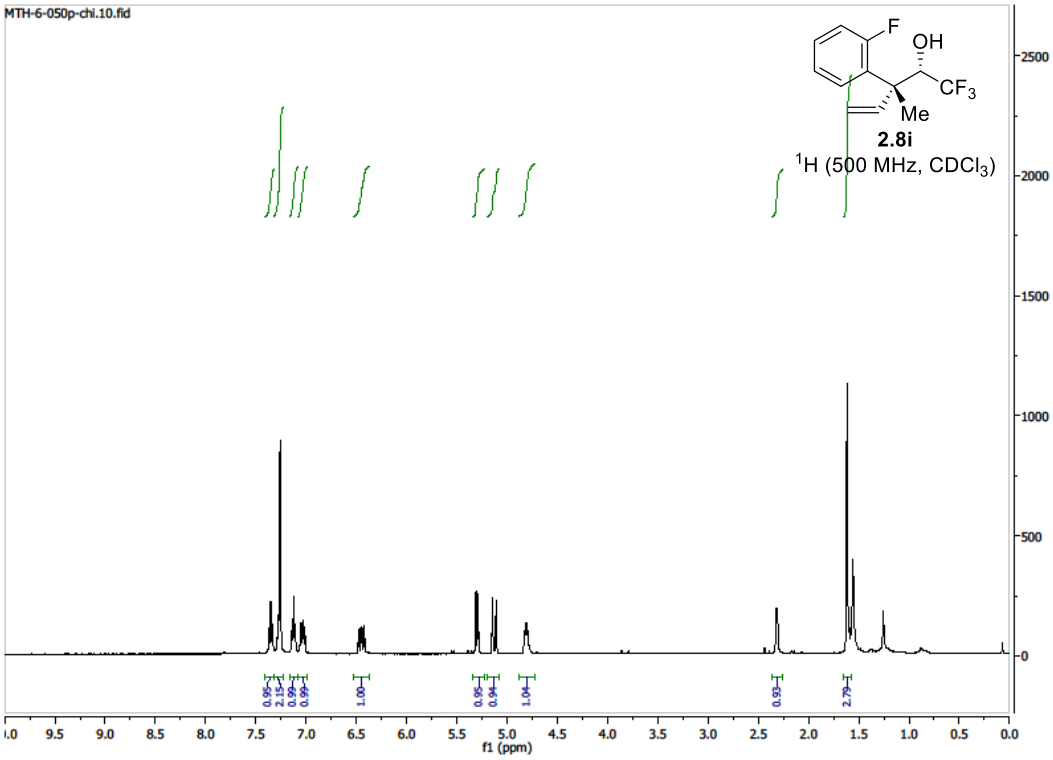
^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (d, *J* = 6.6 Hz), -108.6 (m).

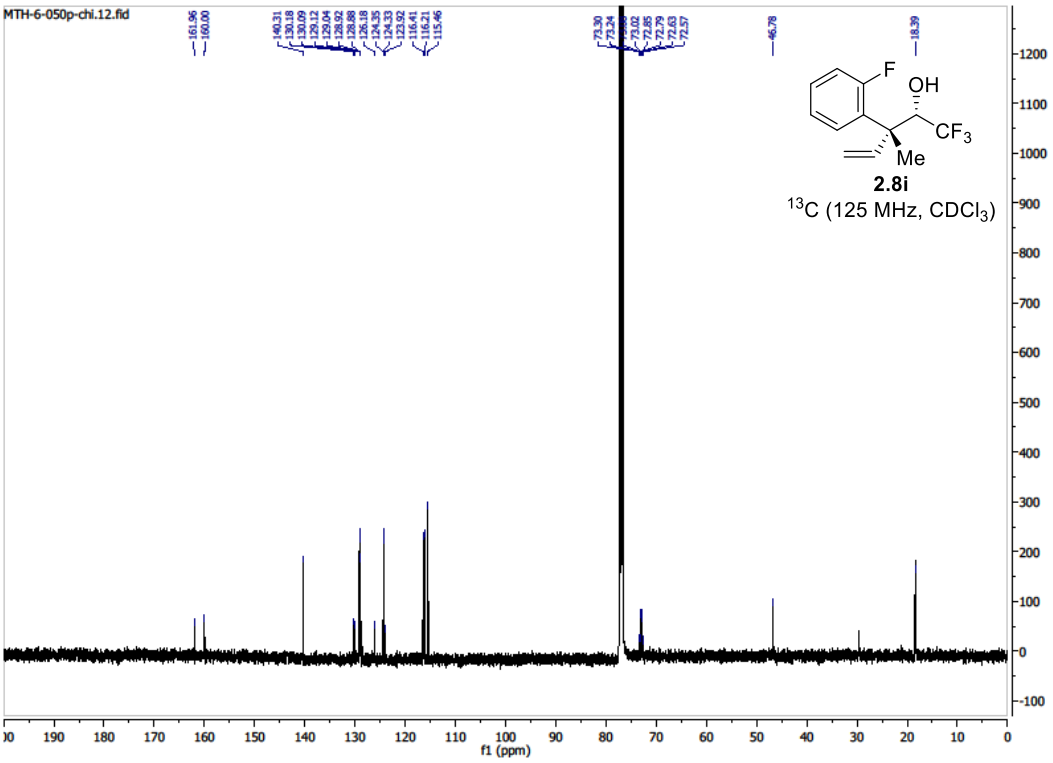
HRMS (CI+, *m/z*) for $C_{12}H_{12}OF_4$: calcd. = 248.0824; found = 248.0827.

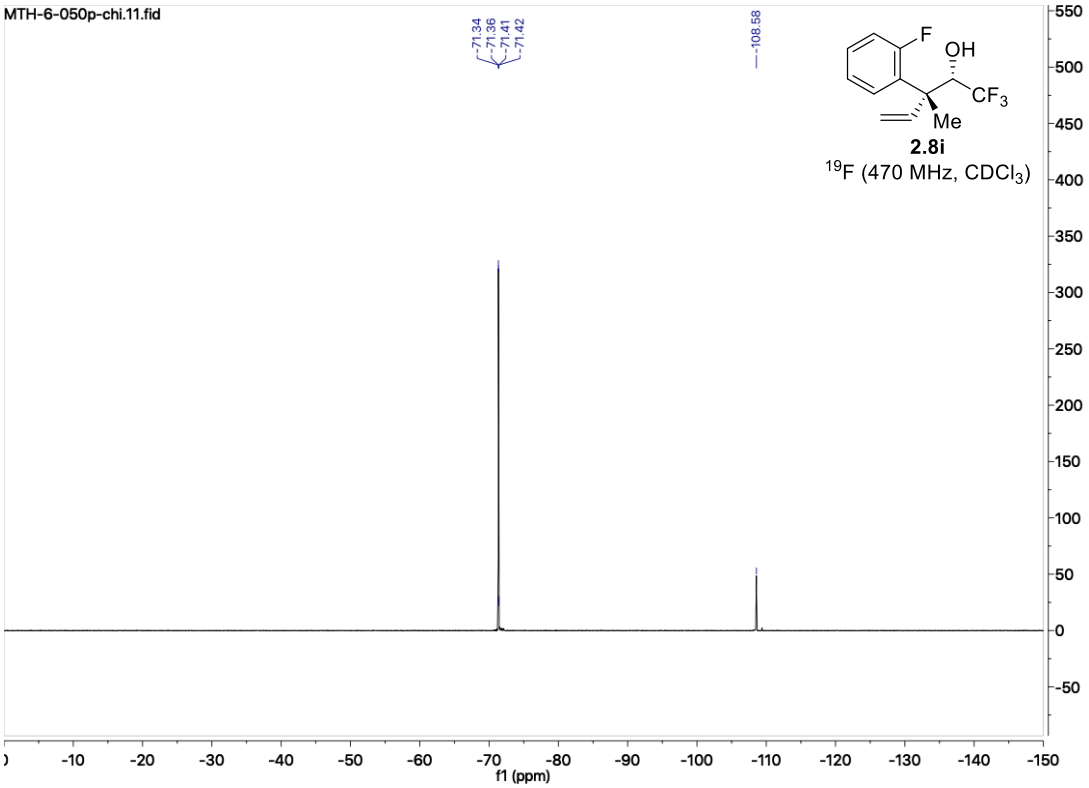
FTIR (neat): 3430, 2931, 2368, 1489, 1451, 1276, 1166, 1103, 929, 810, 757 cm^{-1}.

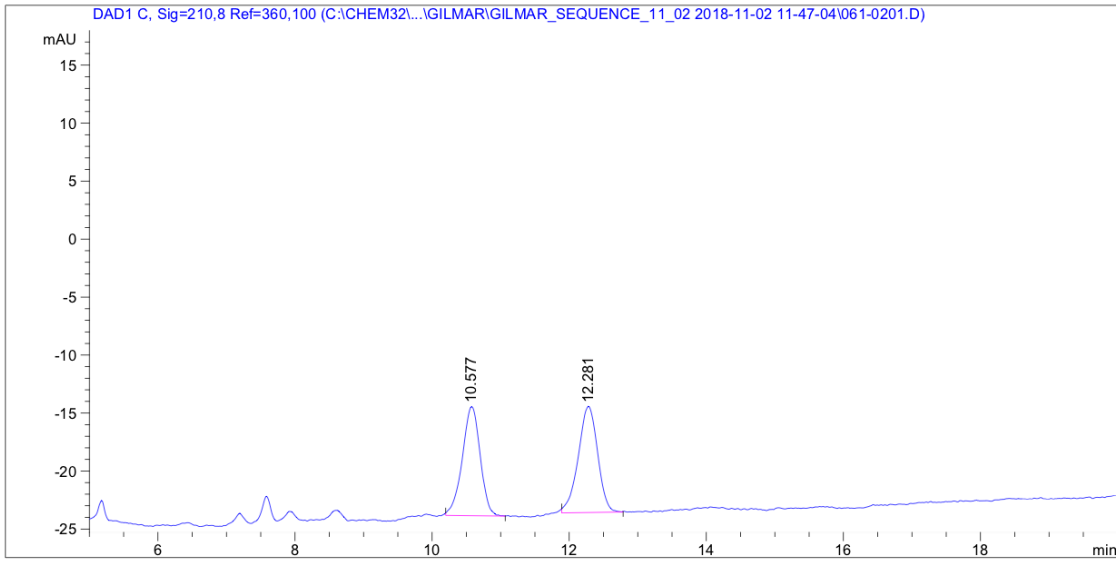
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +16.3 (c = 0.61, $CHCl_3$).

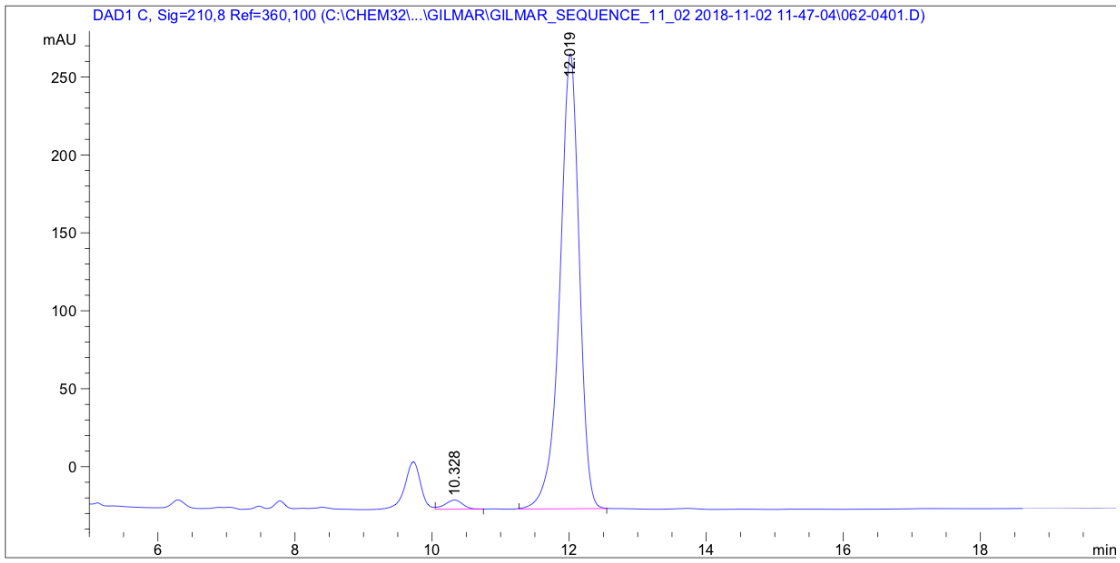

MTH-6-050p-chi.10.fid
F
OH
CF3
Me
2.8i
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-050p-chi.12.fid
F
OH
CF3
Me
2.8i
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-050p-chi.11.fid
-71.34
-71.36
-71.41
-71.42
-108.58
F
OH
CF3
Me
2.8i
19F (470 MHz, CDCl3)
f1 (ppm)

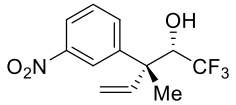


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.577	BB	0.2840	170.87952	9.40205	48.6609
2	12.281	BB	0.2918	180.28415	9.15148	51.3391



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.328	VB	0.2573	103.13152	5.80301	1.7621
2	12.019	BB	0.2998	5749.50146	291.87677	98.2379

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-(3-nitrophenyl)pent-4-en-2-ol (2.8j)



2.8j

1,1-Disubstituted allene **2.6j** (70.1 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:9 EtOAc/hexanes), the title compound **2.8j** (40.7 mg, 0.15 mmol, > 20:1 dr) was obtained as a light yellow oil in 74% yield.

R_f = 0.2 (9:1 Hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (t, *J* = 2.1 Hz, 1H), 8.13 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 6.40 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.43 (d, *J* = 10.9 Hz, 1H), 5.21 (d, *J* = 17.6 Hz, 1H), 4.45 – 4.35 (m, 1H), 2.51 (d, *J* = 5.5 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.3, 146.2, 139.9, 133.3, 129.2, 124.8 (q, *J* = 285 Hz), 122.2, 122.0, 116.9, 75.5 (q, *J* = 28.5 Hz), 47.3, 29.7, 21.1 (q, *J* = 2.46 Hz).

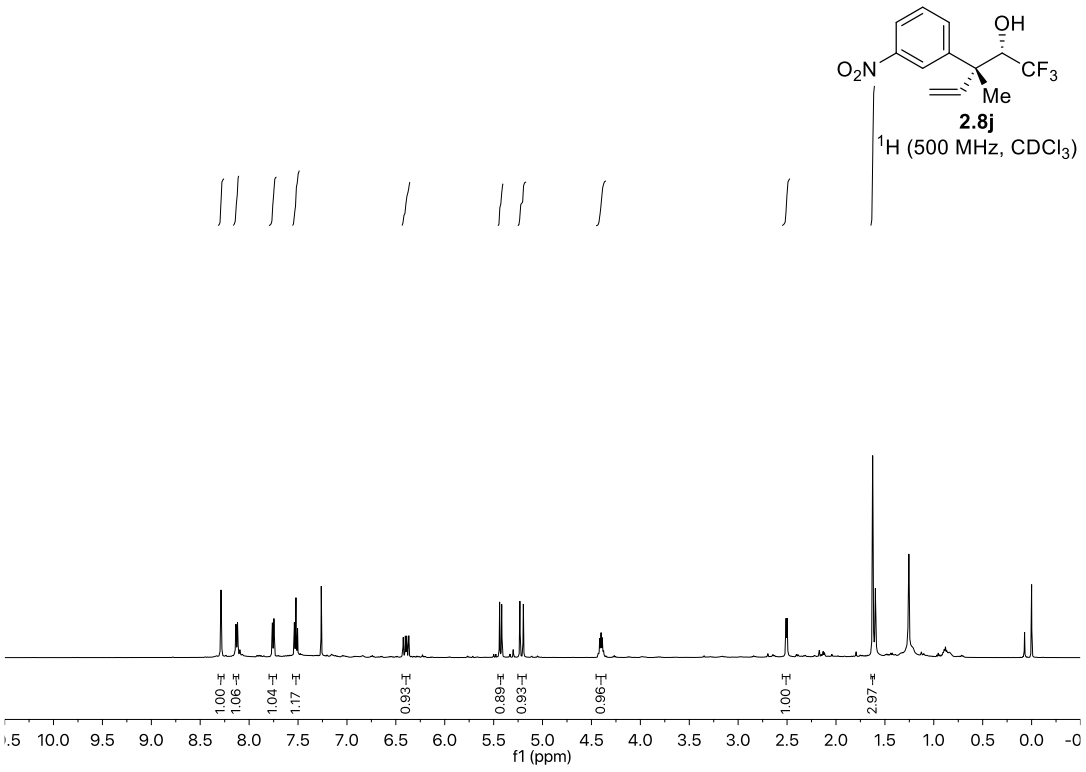
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 7.27 Hz),

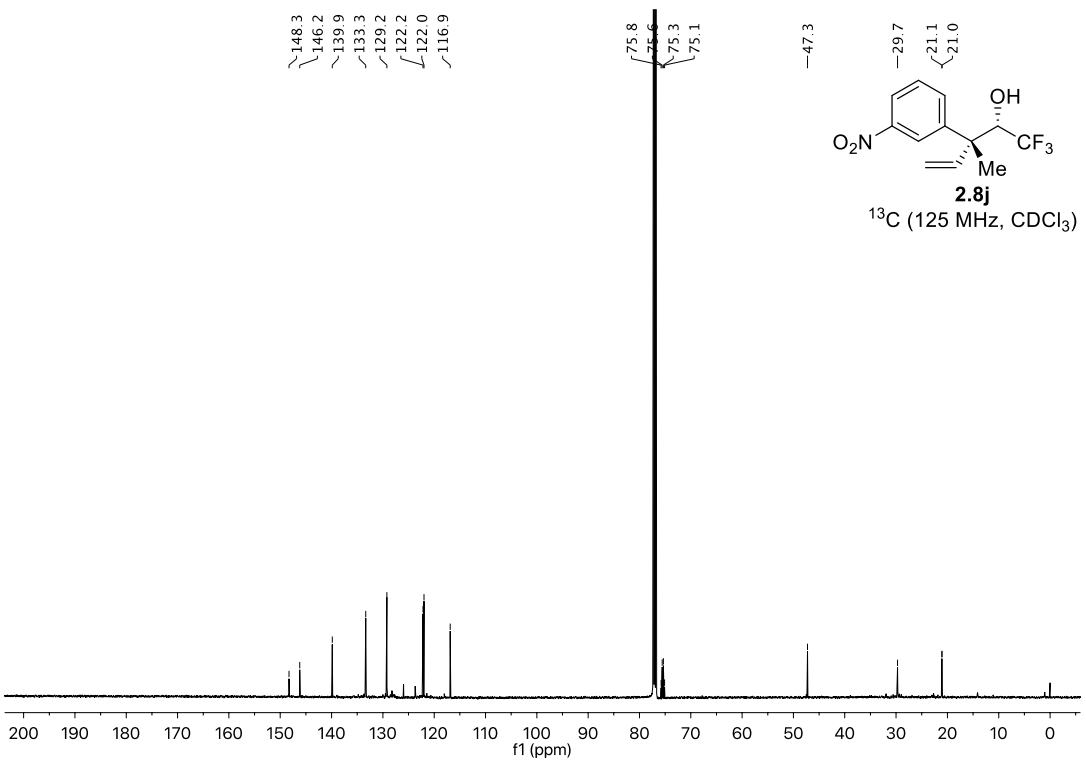
HRMS (CI+H, *m/z*) for $C_{12}H_{13}NO_2F_3$: calcd. = 276.0848; found = 276.0843.

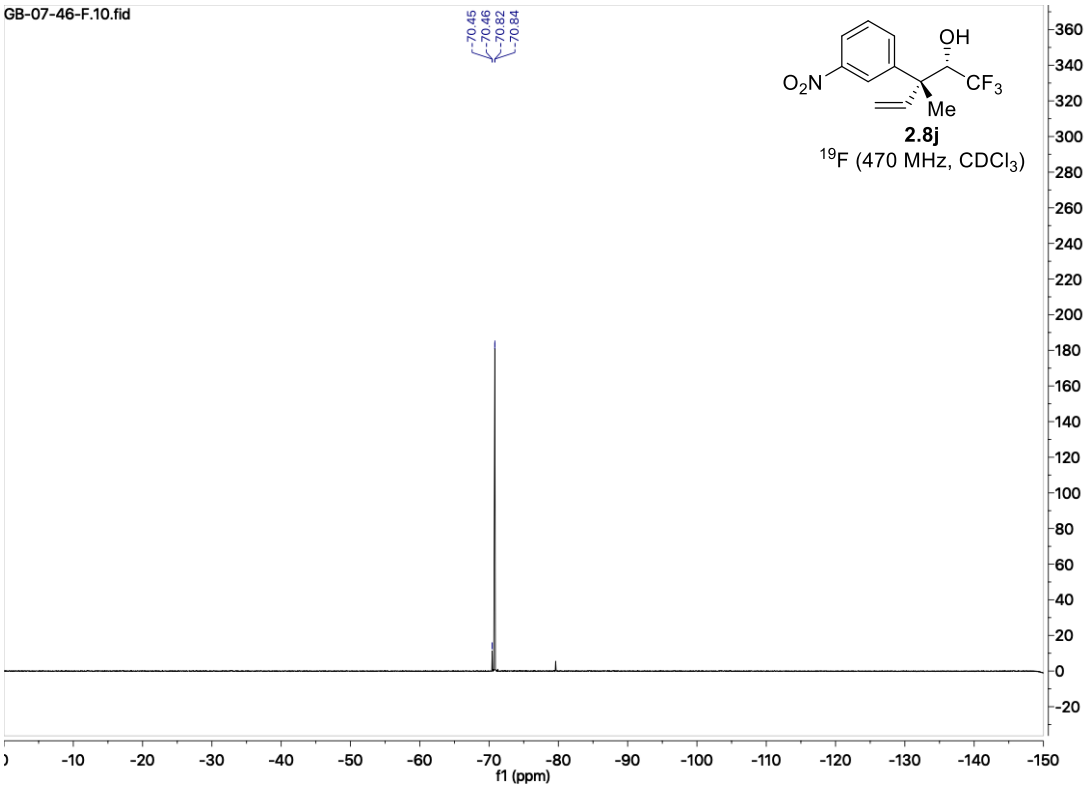
FTIR (neat): 3473, 2922, 2852, 1528, 1349, 1217, 1156, 1091, 928, 693 cm^{-1}.

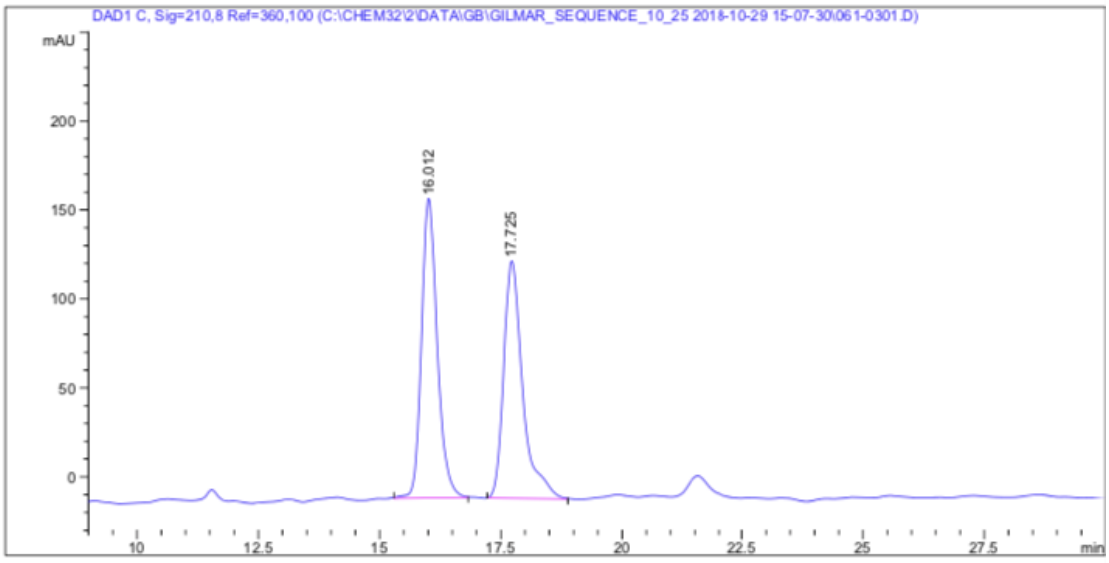
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +5.8 (c = 0.5, $CHCl_3$).

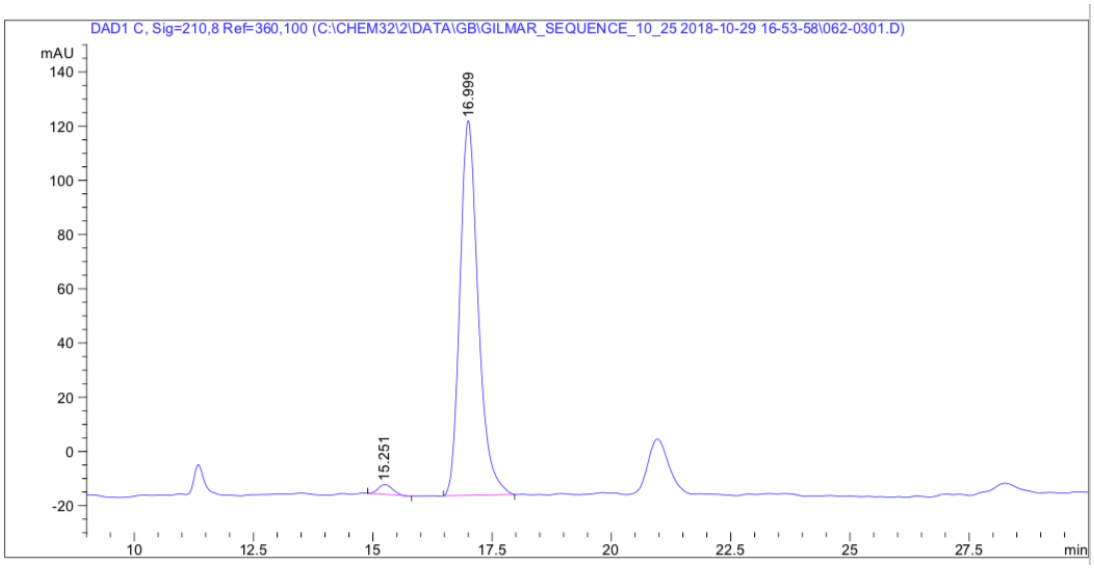

OH
O_2N
CF_3
Me
2.8j
^{1}H (500 MHz, $CDCl_3$)
1.00
1.06
1.04
1.17
0.93
0.89
0.93
0.96
1.00
2.97
f1 (ppm)


148.3
146.2
139.9
133.3
129.2
122.2
122.0
116.9
75.8
75.6
75.3
75.1
47.3
29.7
21.1
21.0
OH
O_2N
CF_3
Me
2.8j
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)


GB-07-46-F.10.fid
-70.45
-70.46
-70.82
-70.84
OH
O_2N
CF_3
Me
2.8j
^{19}F (470 MHz, $CDCl_3$)
f1 (ppm)

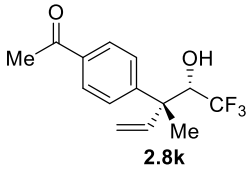


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.012	BB	0.3429	3790.50903	168.21773	50.9917
2	17.725	BB	0.4109	3643.07642	133.26028	49.0083
Totals :				7433.58545	301.47801	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.251	BB	0.2966	74.57161	3.64580	1.9835
2	16.999	BB	0.4051	3684.99146	138.21021	98.0165
Totals :				3759.56306	141.85601	

1-(4-((3*R*,4*S*)-5,5,5-trifluoro-4-hydroxy-3-methylpent-1-en-3-yl)phenyl)ethan-1-one (2.8k)



2.8k

1,1-Disubstituted allene **2.6k** (69 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:5 EtOAc/hexanes), the title compound **2.8k** (46.8 mg, 0.17 mmol, 20:1 dr) was obtained as a light yellow solid in 86% yield.

R_f = 0.14 (5:1 Hexanes : Ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 – 7.91 (m, 2H), 7.51 – 7.48 (m, 2H), 6.38 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.39 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 17.5 Hz, 1H), 4.42 (qd, *J* = 7.2, 5.5 Hz, 1H), 2.59 (s, 3H), 2.35 (d, *J* = 5.7 Hz, 1H), 1.59 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.7, 149.2, 140.3, 135.7, 128.5, 127.2, 124.9 (q, *J* = 282 Hz), 116.4, 75.5 (q, *J* = 28 Hz), 47.5, 26.6, 20.7 (q, 2.6 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 7.1 Hz).

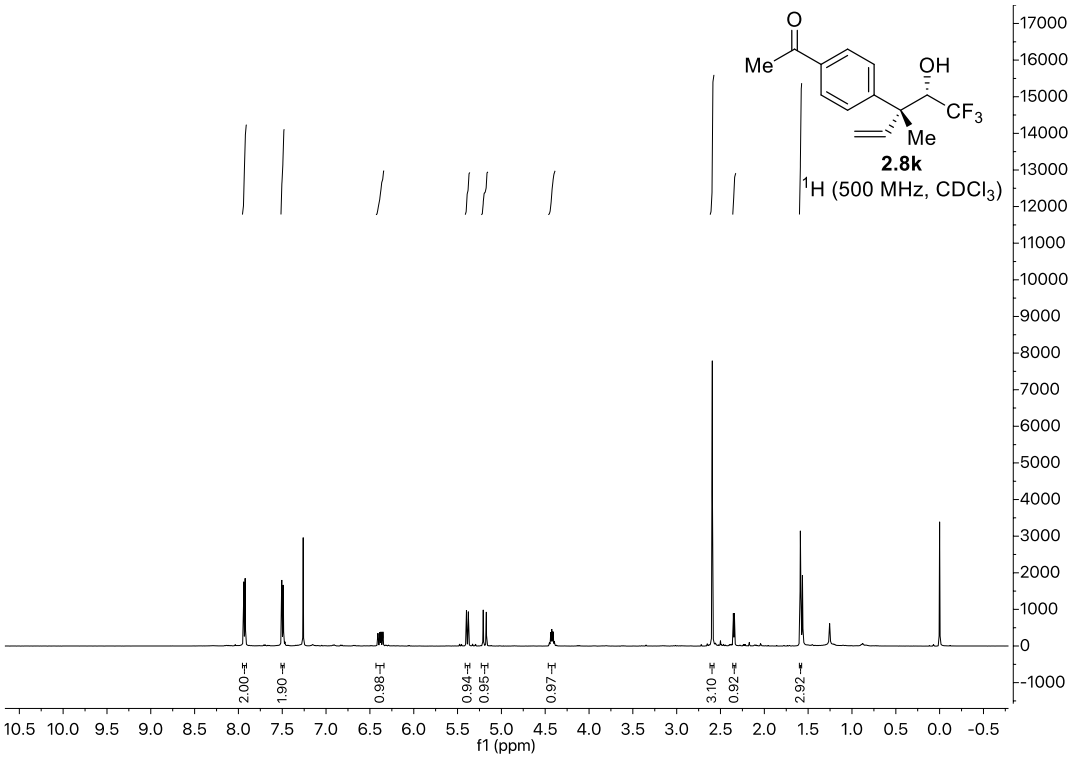
HRMS (ESI + H, *m/z*) for $C_{14}H_{16}F_3O_2$: calcd. = 273.1097; found = 273.100.

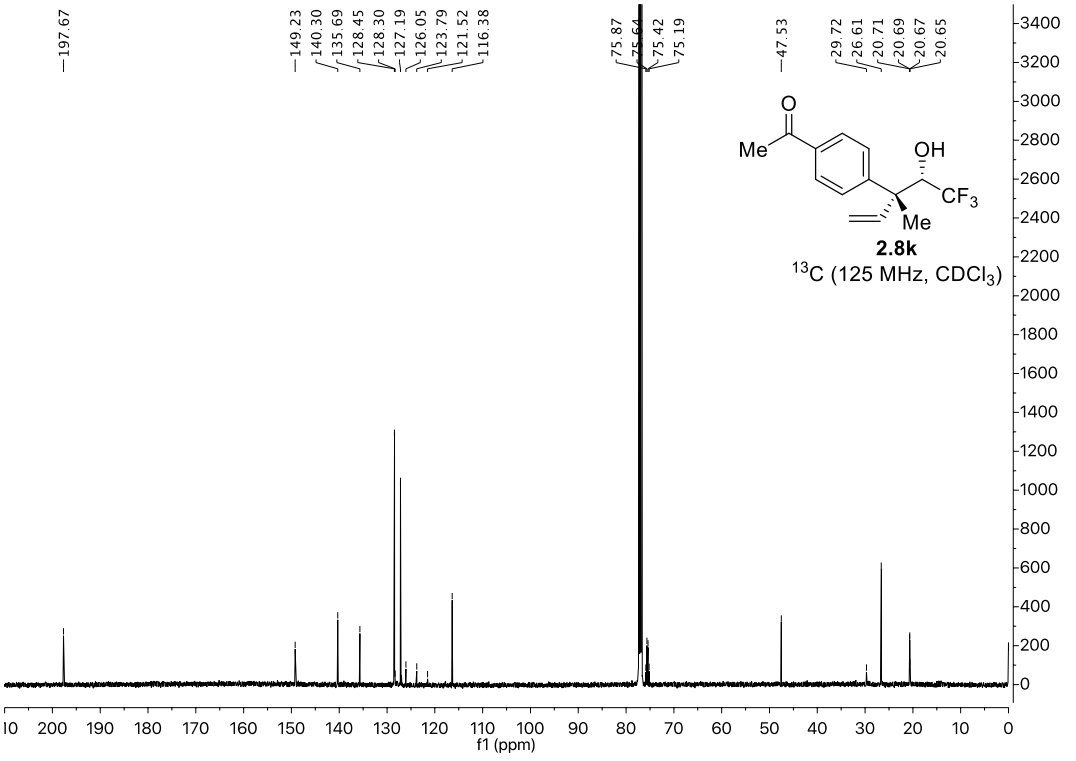
FTIR (neat): 3427, 2922, 2853, 1674, 1605, 1407, 1360, 1271, 1154, 1121, 1095, 1014, 960, 822, 692 cm^{-1}.

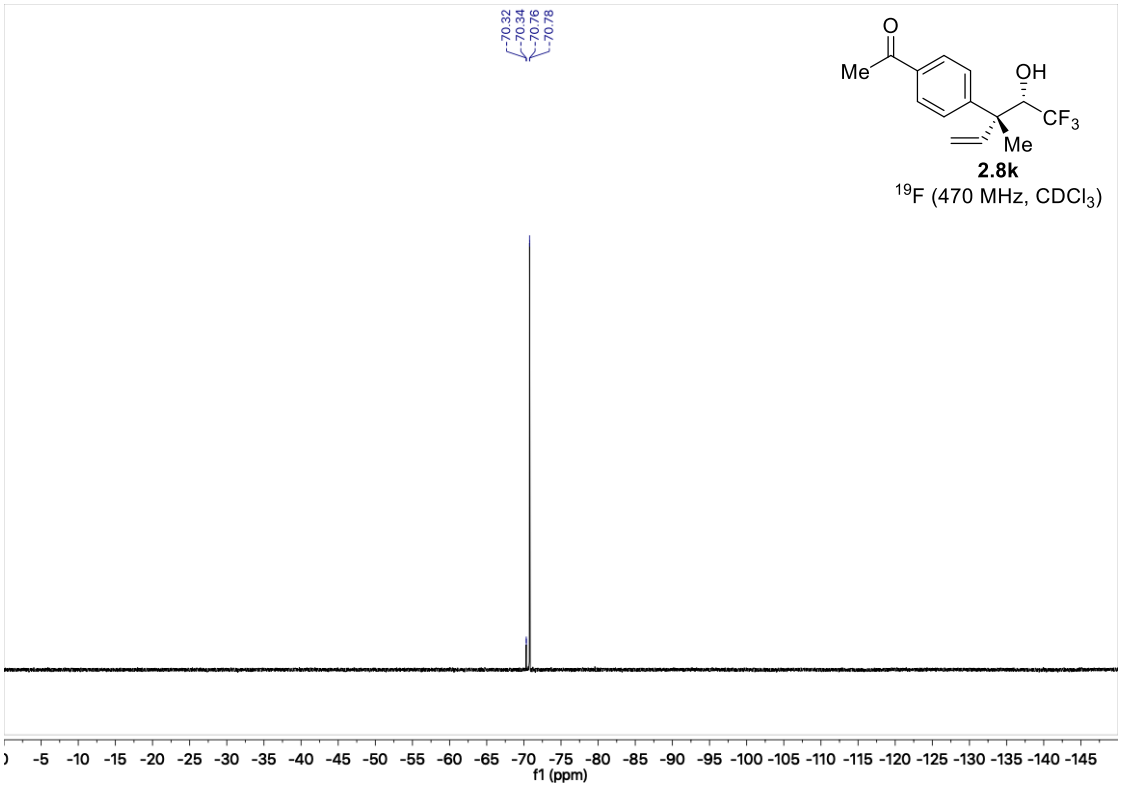
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

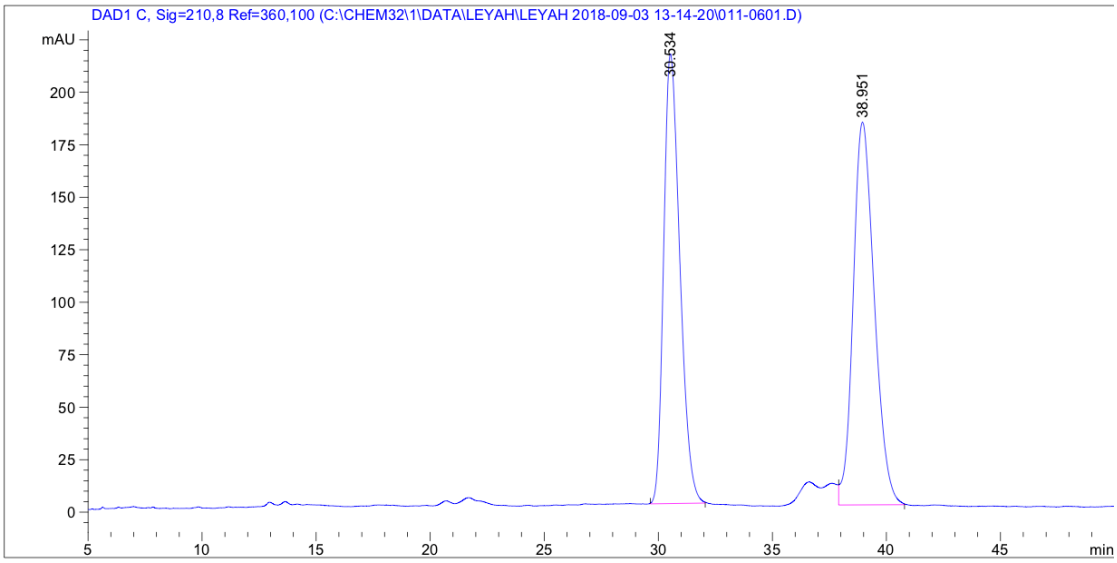
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -16 (c = 0.5, $CHCl_3$).

MP = 62-65 °C

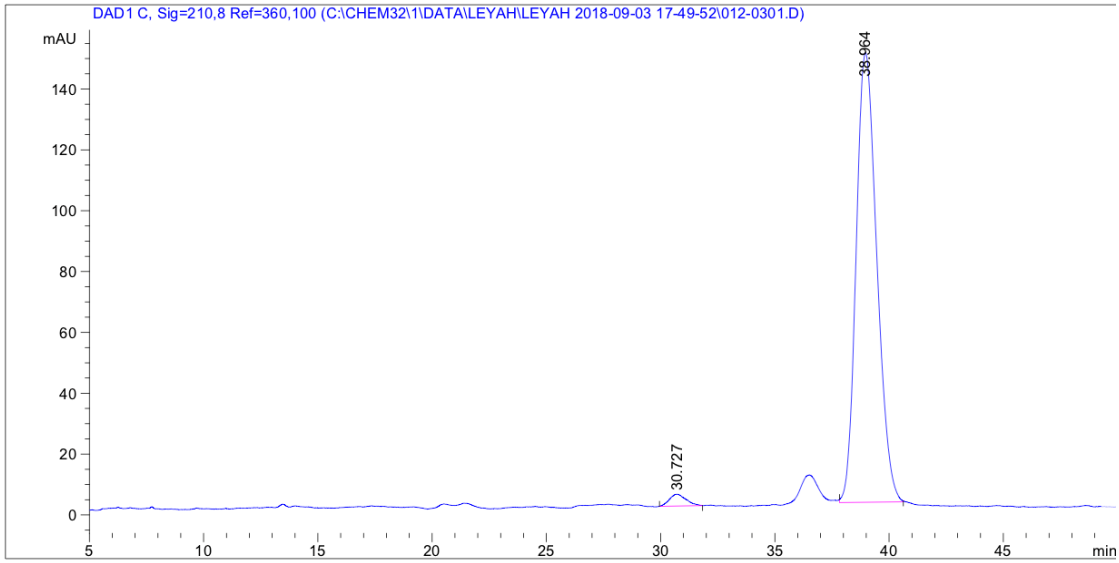

Me
O
OH
CF3
Me
2.8k
1H (500 MHz, CDCl3)
2.00
1.90
0.98
0.94
0.95
0.97
3.10
0.92
2.92
f1 (ppm)


197.67
149.23
140.30
135.69
128.45
128.30
127.19
126.05
123.79
121.52
116.38
75.87
75.64
75.42
75.19
47.53
29.72
26.61
20.71
20.69
20.67
20.65
Me
O
OH
CF3
Me
2.8k
13C (125 MHz, CDCl3)
f1 (ppm)


-70.32
-70.34
-70.76
-70.78
O
Me
OH
CF3
Me
2.8k
19F (470 MHz, CDCl3)
-5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)

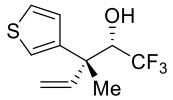


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.534	BB	0.7548	1.05600e4	214.35287	47.3434
2	38.951	VB	0.9757	1.17451e4	182.28189	52.6566



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.727	BB	0.6056	196.12804	3.88055	2.0714
2	38.964	BB	0.9366	9272.20703	147.66473	97.9286

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-(thiophen-3-yl)pent-4-en-2-ol (2.8l)



2.8l

1,1-Disubstituted allene **2.6l** (54.5 mg, 0.4 mmol) was subjected to general procedure K using a reaction time of 8 hours. Upon flash column chromatography (SiO_2, 5:95 EtOAc/hexanes), the title compound **2.8l** (32.3 mg, 0.14 mmol, 13:1 dr) was obtained as a clear oil in 68% yield. Note: the shorter reaction time was required due to the formation of overreduced product under standard reaction times. Additionally instability on chiral column was observed.

R_f = 0.3 (4:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (m, 1H), 7.15 (m, 1H), 7.08 (m, 1H), 6.35 (dd, *J* = 6.4, 17.6 Hz, 1H), 5.31 (d, *J* = 10.9 Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 4.23 (dq, *J* = 7.3, 6.2 Hz, 1H), 2.23 (d, *J* = 5.8 Hz, 1H), 1.58 (q, *J* = 1.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.5, 140.2, 126.5, 126.0, 124.9 (q, *J* = 283.5 Hz), 121.8, 115.8, 75.8 (q, *J* = 28.3 Hz), 45.9, 21.4 (q, *J* = 2.4 Hz).

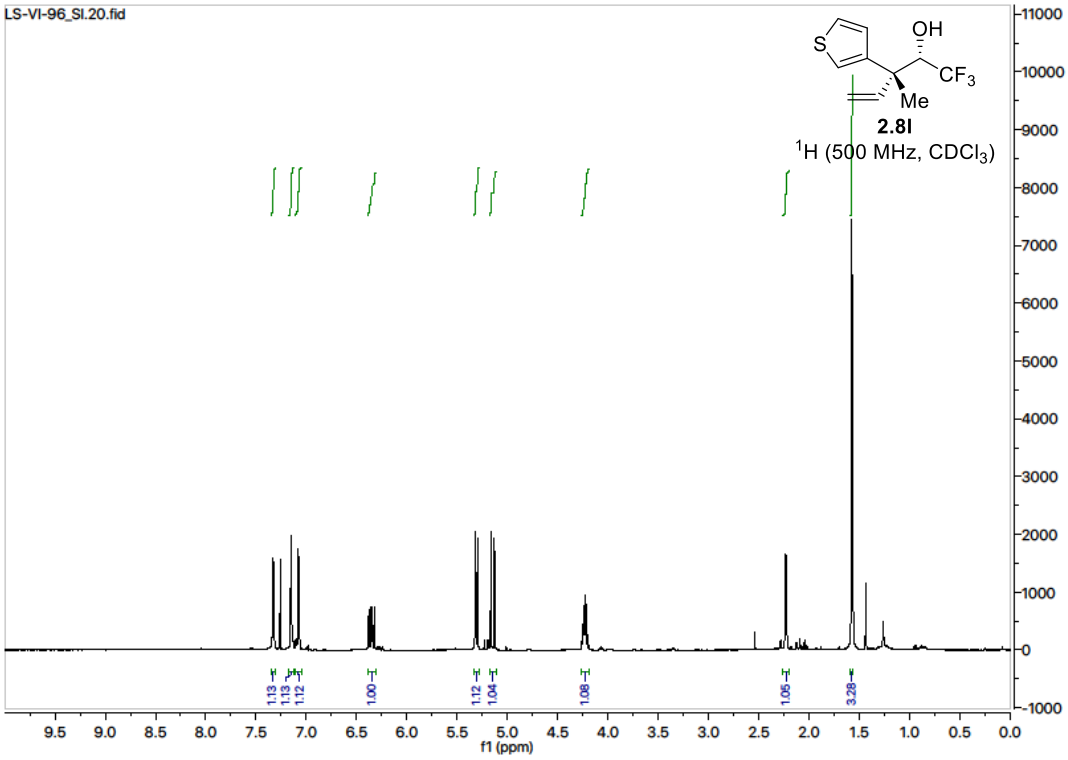
^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.1 (d, *J* = 7.3 Hz).

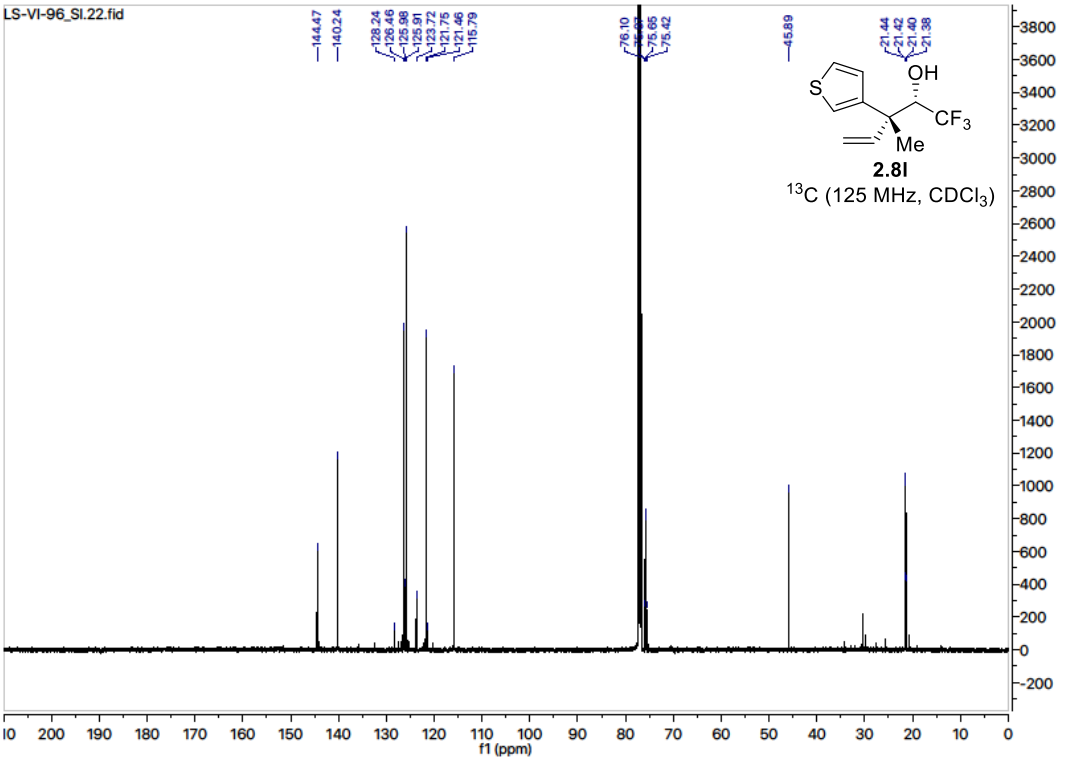
HRMS (CI+, *m/z*) for $C_{10}H_{11}F_3OS$: calcd. = 236.0483; found = 236.0479.

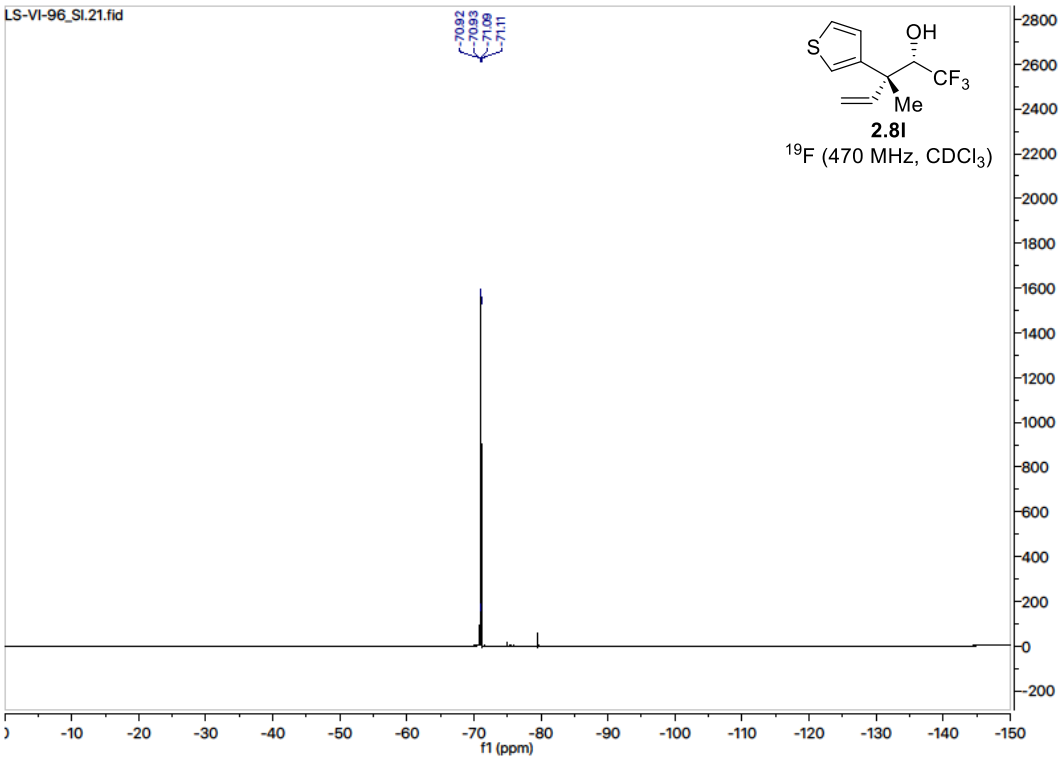
FTIR (neat): 3500, 2950, 2900, 1450, 1400, 1300, 1150, 1100, 1000, 900, 800, 700, 650 cm^{-1}.

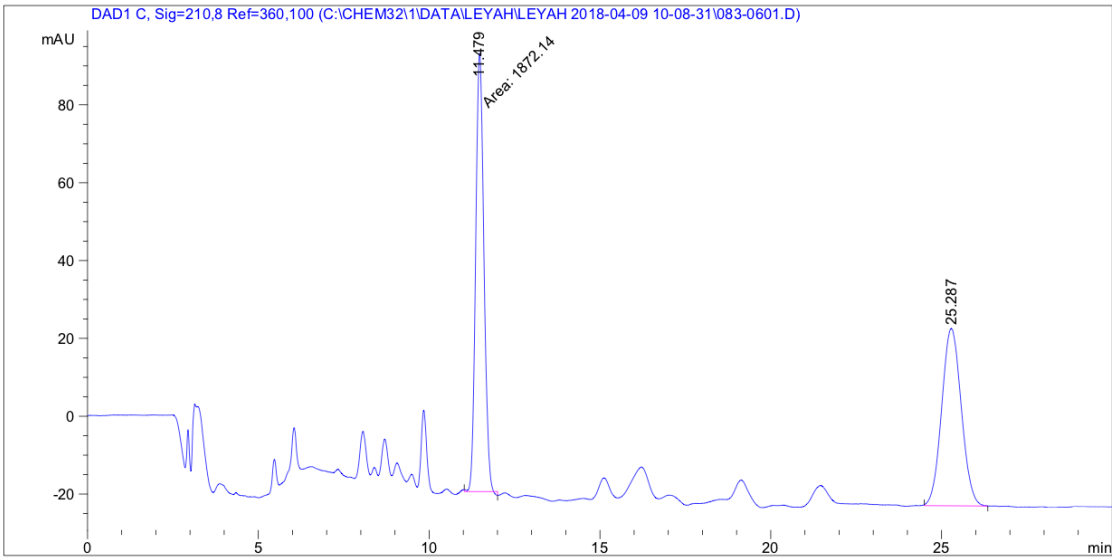
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 94%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -17.5 (c = 1.1, $CHCl_3$).

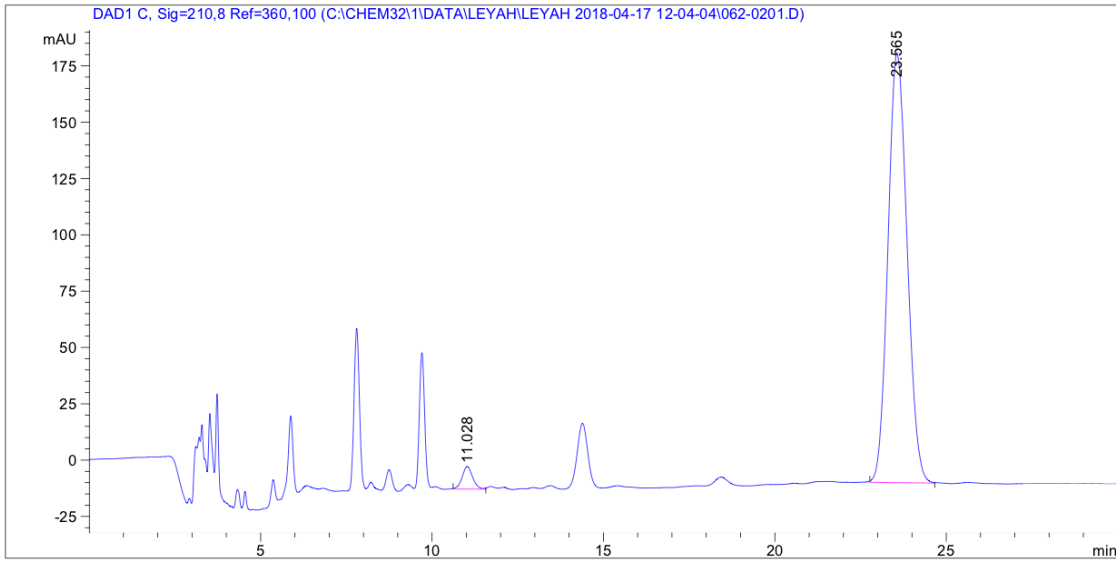

LS-VI-96_SI.20.fid
OH
S
CF3
Me
2.8l
1H (500 MHz, CDCl3)
f1 (ppm)


LS-VI-96_SI.22.fid
144.47
140.24
128.24
126.46
125.98
125.91
123.72
121.75
121.46
115.79
76.10
75.65
75.42
45.89
21.44
21.42
21.40
21.38
OH
S
CF3
Me
2.8l
13C (125 MHz, CDCl3)
f1 (ppm)


LS-VI-96_SI.21.fid
70.92
70.93
71.09
71.11
OH
S
CF3
Me
2.8l
19F (470 MHz, CDCl3)
f1 (ppm)

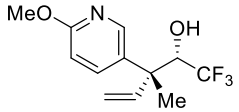


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.479	MM	0.2770	1872.14246	112.63503	50.7289
2	25.287	BB	0.6258	1818.34070	45.54578	49.2711



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.028	BB	0.3278	212.51180	10.00615	2.7979
2	23.565	BB	0.6059	7382.94531	190.60022	97.2021

(2*S*,3*R*)-1,1,1-trifluoro-3-(6-methoxypyridin-3-yl)-3-methylpent-4-en-2-ol (2.8m)



2.8m

1,1-Disubstituted allene **2.6m** (64 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:9 EtOAc/hexanes), the title compound **2.8m** (35.5 mg, 0.14 mmol, 19:1 dr) was obtained as a yellow oil in 68% yield.

R_f = 0.19 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 2.7 Hz, 1H), 7.60 (dd, *J* = 2.7, 9.5 Hz, 1H), 6.72 (d, *J* = 9.5 Hz, 1H), 6.34 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.34 (d, *J* = 10.9 Hz, 1H), 5.15 (d, *J* = 17.7 Hz, 1H), 4.27 (dq, *J* = 6.5 Hz, 1H), 3.92 (s, 3H), 2.41 (d, *J* = 6.5 Hz, 1H, O*H*), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0, 145.5, 140.5, 137.8, 131.6, 124.9 (q, *J* = 277 Hz), 116.0, 110.4, 75.5 (q, *J* = 30 Hz), 53.5, 45.5, 20.9.

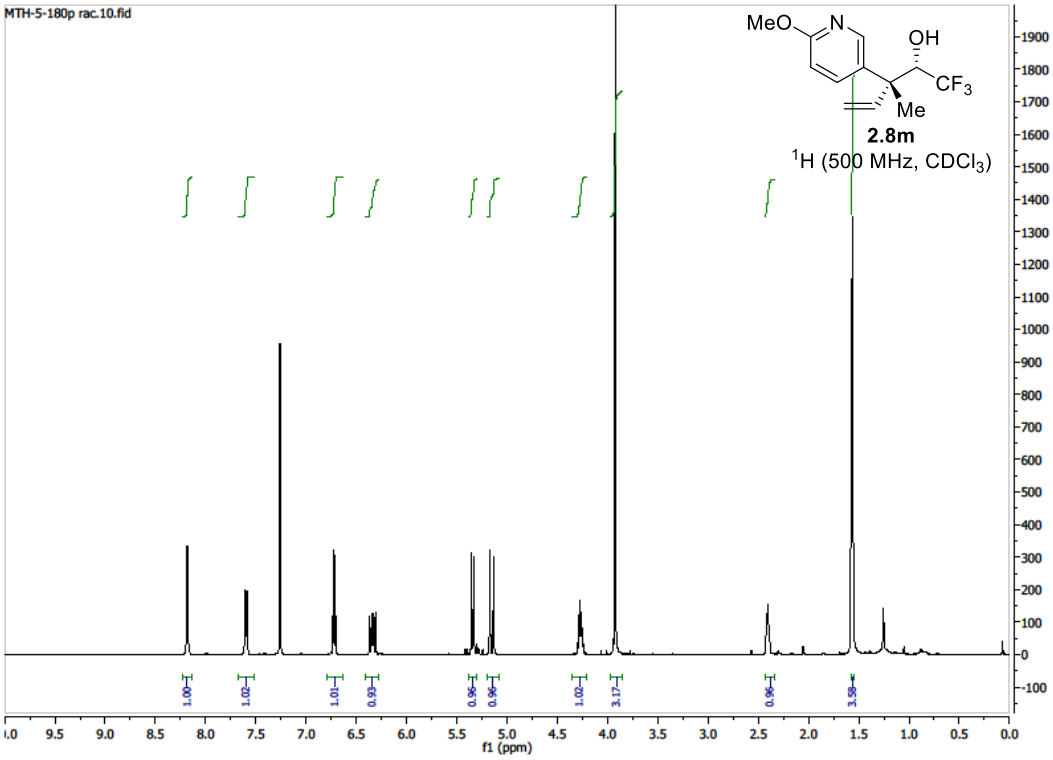
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 6.8 Hz).

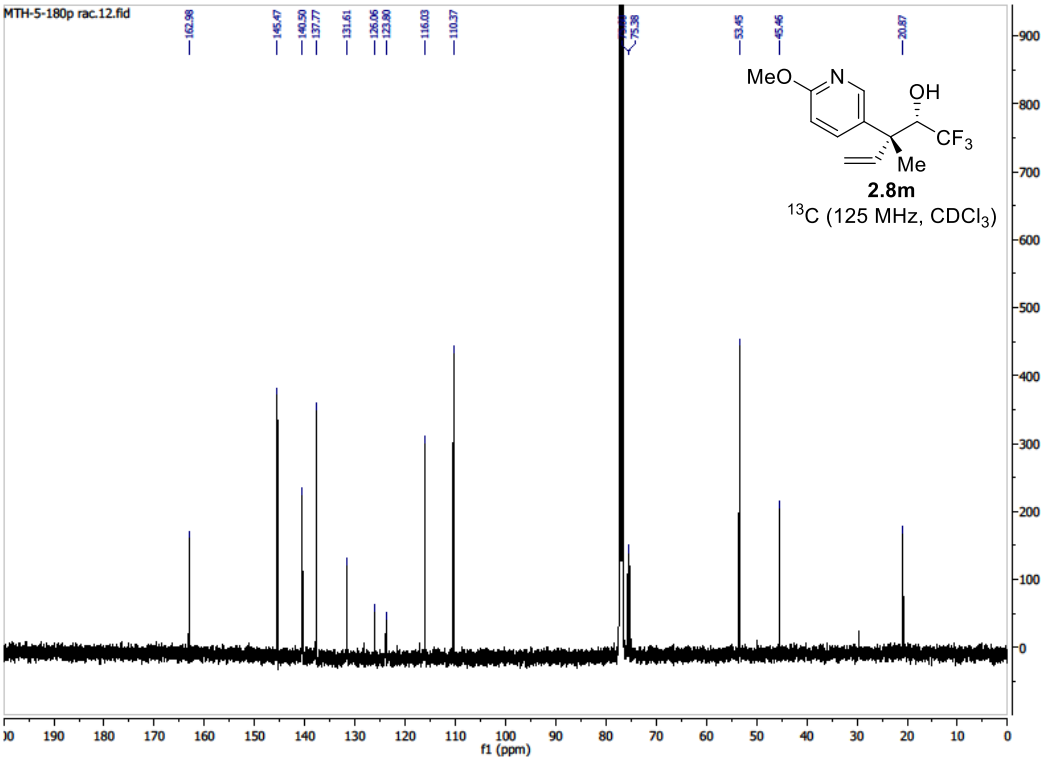
HRMS (ESI+H, *m/z*) for $C_{12}H_{14}F_3NO_2$: calcd. = 262.1049; found = 262.1051.

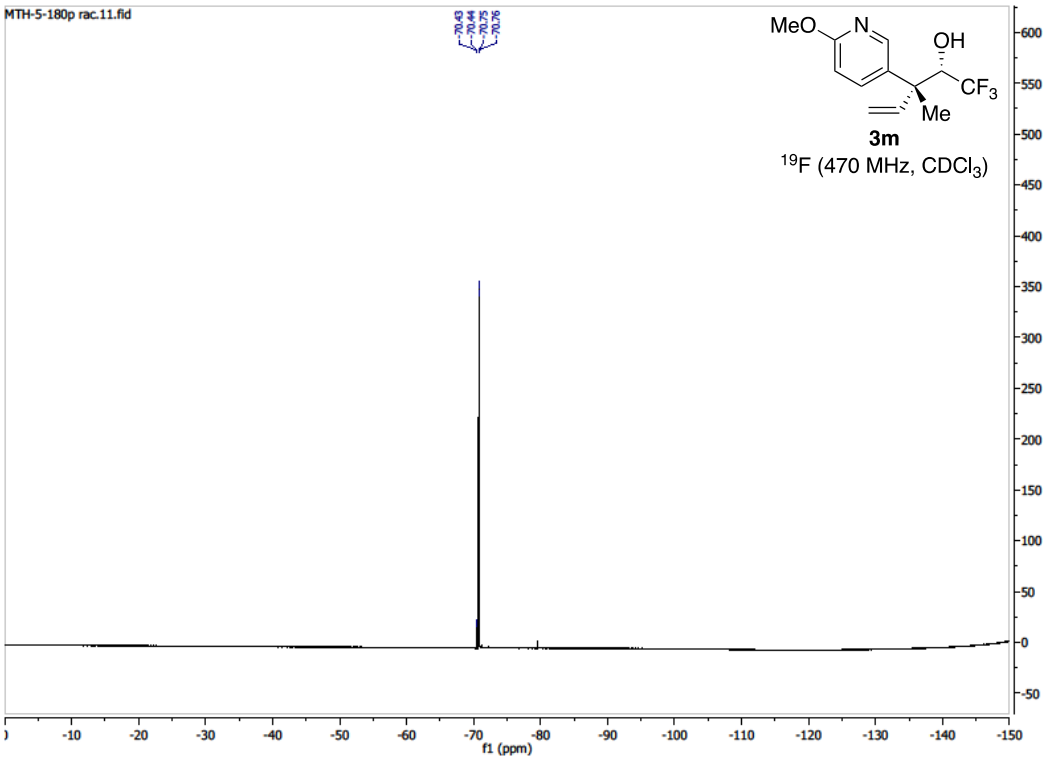
FTIR (neat): 3375, 2981, 2359, 1606, 1498, 1385, 1272, 1158, 1026, 927, 828 cm^{-1}.

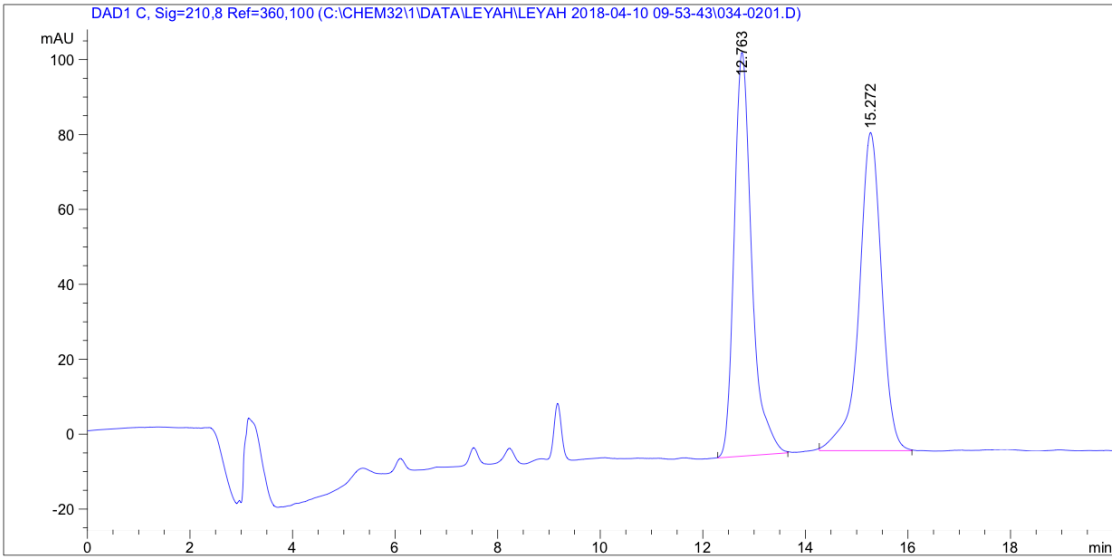
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 97%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -60 (c = 0.25, $CHCl_3$).

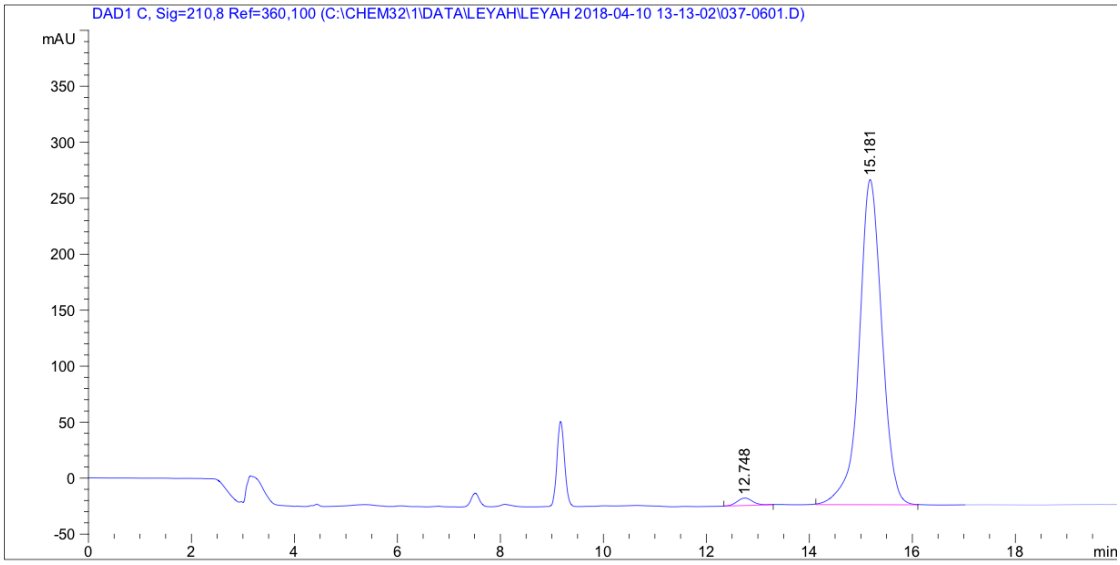

MTH-5-180p rac.10.fid
MeO
N
OH
CF3
Me
2.8m
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-180p rac.12.fid
MeO
N
OH
CF3
Me
2.8m
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-5-180p rac.11.fid
-70.43
-70.44
-70.75
-70.76
MeO
N
OH
CF3
Me
3m
19F (470 MHz, CDCl3)
f1 (ppm)

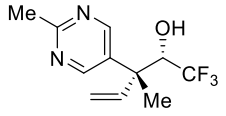


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.763	BB	0.3629	2557.54541	107.76994	49.6003
2	15.272	BB	0.4672	2598.76245	84.88286	50.3997



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.748	BB	0.3225	139.54668	6.66001	1.5451
2	15.181	BB	0.4673	8892.24414	290.34576	98.4549

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-(2-methylpyrimidin-5-yl)pent-4-en-2-ol (2.8n)



2.8n

1,1-Disubstituted allene **2.6n** (58 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 2:1 EtOAc:hexanes), the title compound **2.8n** (33.8 mg, 0.14 mmol, 15:1 dr) was obtained as a yellow solid in 69% yield.

R_f = 0.31 (1:2 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (s, 2H), 6.34 (dd, *J* = 11.8, 17.8 Hz, 1H), 5.35 (d, *J* = 11.8 Hz, 1H), 5.13 (d, *J* = 17.8 Hz, 1H), 4.19 (q, *J* = 7.6 Hz, 1H), 2.63 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 156.0, 138.9, 134.1, 124.9 (q, *J* = 286.7 Hz), 117.3, 75.1 (q, *J* = 29.0 Hz), 44.6, 25.3, 21.2.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (d, *J* = 7.6 Hz).

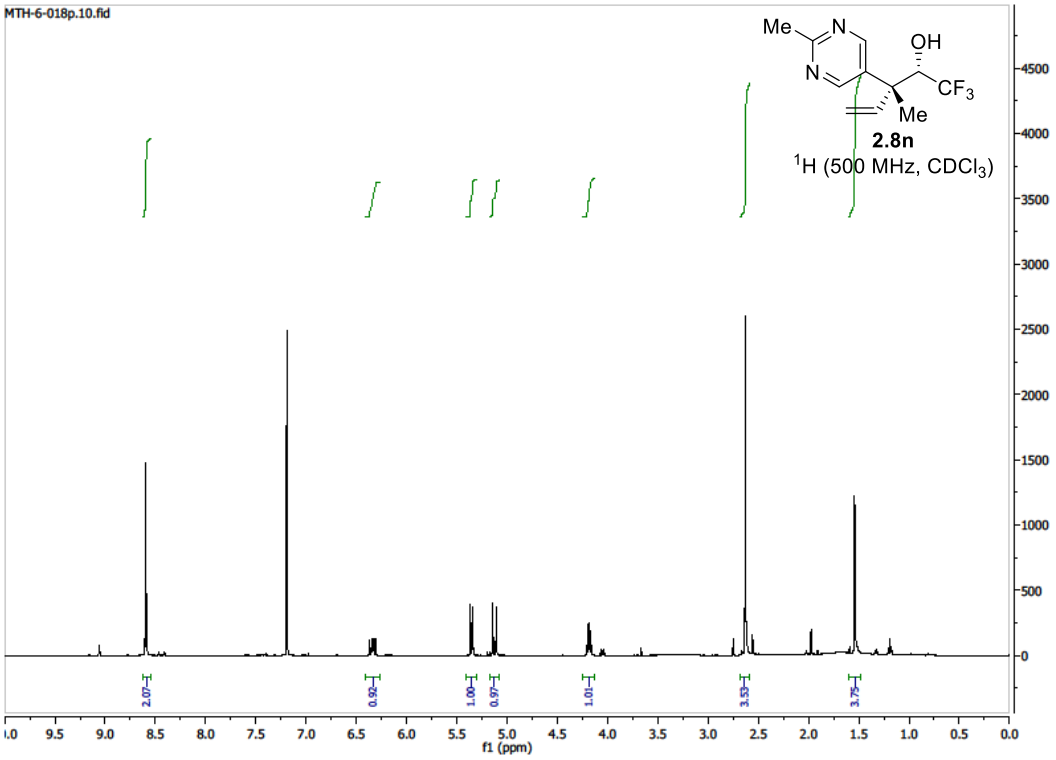
HRMS (CI+, *m/z*) for $C_{11}H_{13}F_3N_2O$: calcd. = 247.1053; found = 247.1052.

FTIR (neat): 3158, 2937, 2364, 1589, 1451, 1271, 1156, 1127, 931, 753, 698 cm^{-1}.

HPLC: (Chiralcel column OD-3, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 96%.

$[\alpha]_D^{24}$= -41 (c = 0.25, $CHCl_3$).

MP = 74-77 °C


MTH-6-018p.10.fid
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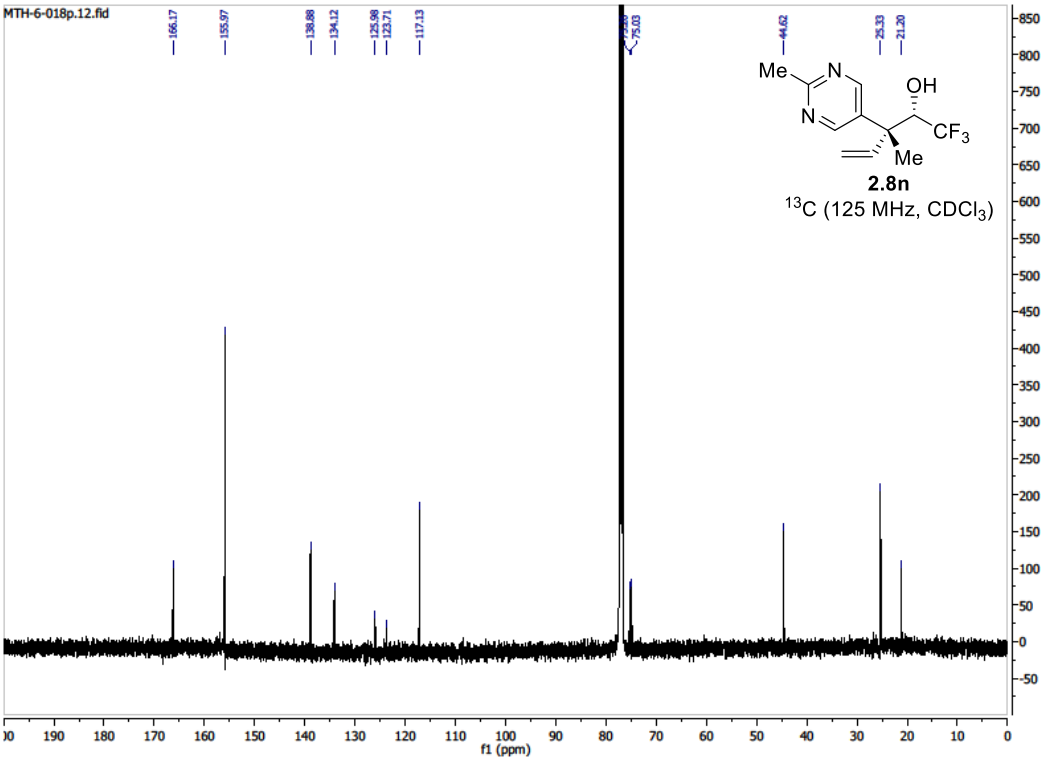
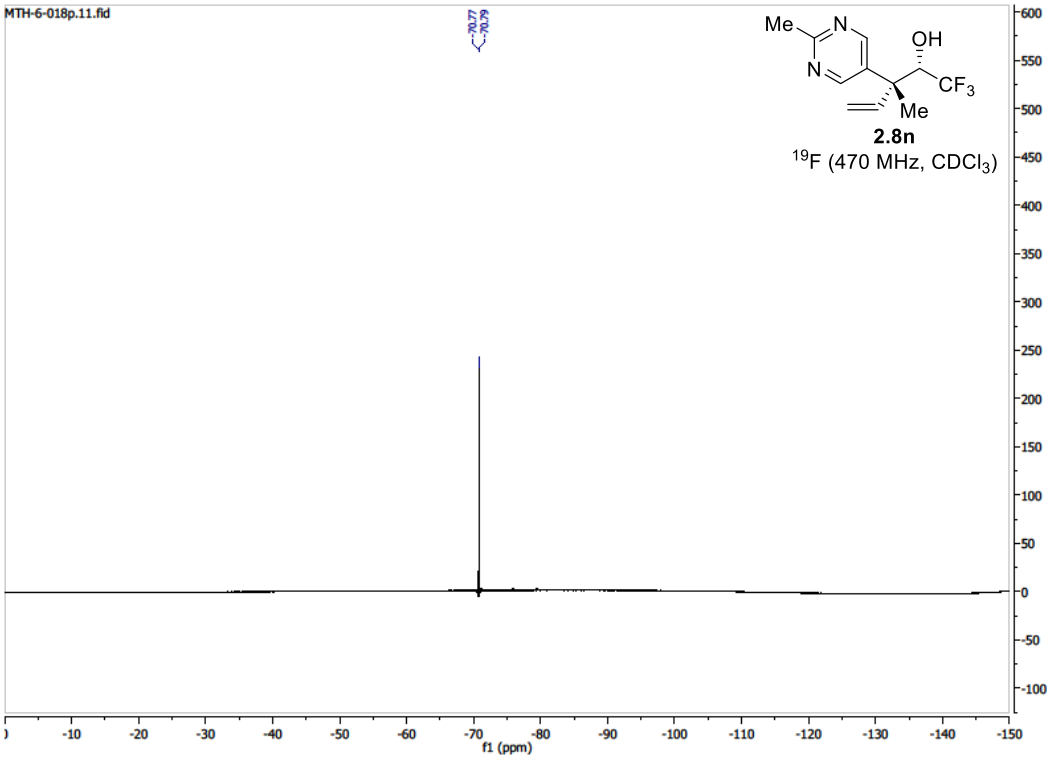
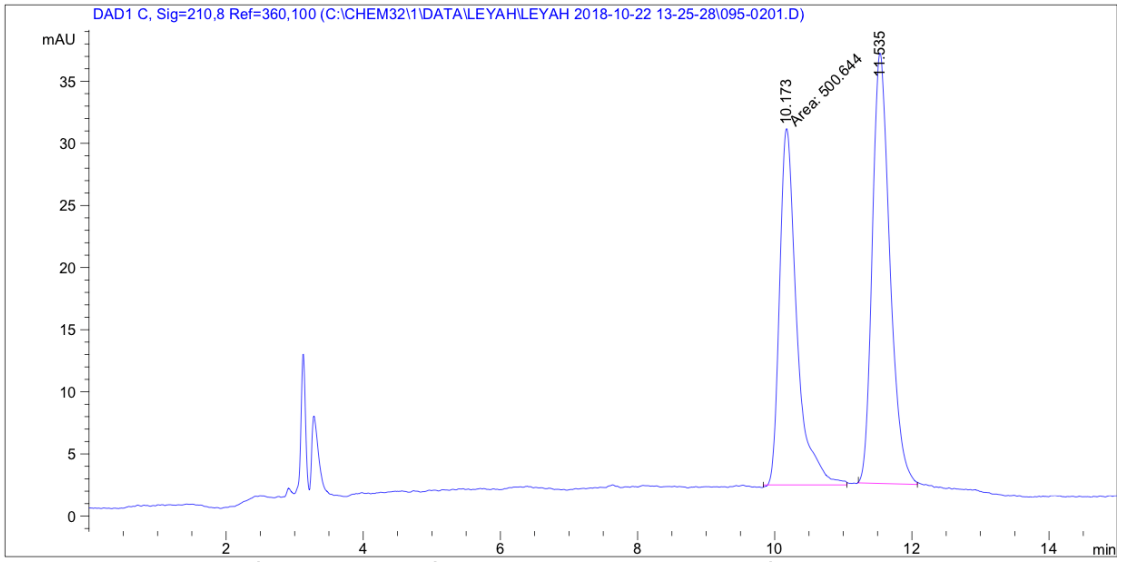
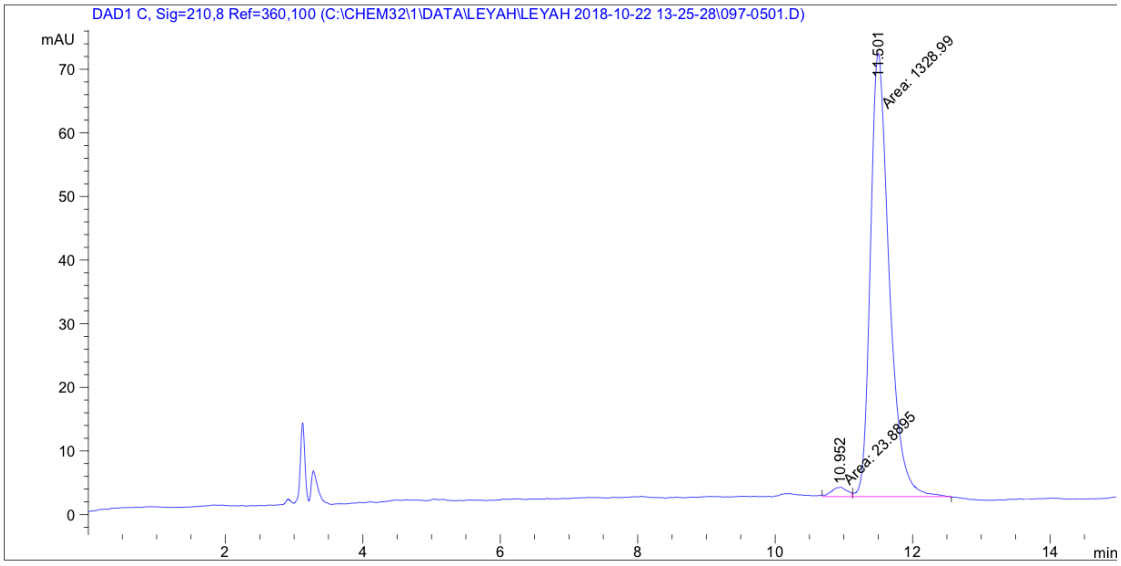
N
N
OH
CF3
Me
2.8n
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-018p.12.fid
166.17
155.97
138.88
134.12
125.98
123.71
117.13
77.03
44.62
25.33
21.20
Me
N
N
OH
CF3
Me
2.8n
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-018p.11.fid
-70.77
-70.79
Me
N
N
OH
CF3
Me
2.8n
19F (470 MHz, CDCl3)
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

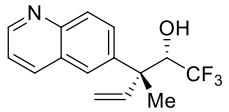


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.173	MM	0.2908	500.64371	28.68983	44.7344
2	11.535	BB	0.2702	618.50317	34.66129	55.2656



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.952	MF	0.2715	23.88947	1.46642	1.7658
2	11.501	FM	0.3177	1328.98999	69.72881	98.2342

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-(quinolin-6-yl)pent-4-en-2-ol (2.8o)



2.8o

1,1-Disubstituted allene **2.6o** (72 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 1:2 EtOAc/hexanes), the title compound **2.8o** (39.2 mg, 0.14 mmol, >20:1 dr) was obtained as a light yellow solid in 70% yield.

R_f = 0.11 (2:1 Hexanes : Ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (t, *J* = 2.1 Hz, 1H), 8.13 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 6.40 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.43 (d, *J* = 10.9 Hz, 1H), 5.21 (d, *J* = 17.6 Hz, 1H), 4.45 – 4.35 (m, 1H), 2.51 (d, *J* = 5.5 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.3, 146.8, 142.9, 140.5, 136.6, 129.0, 128.9, 127.9, 125.8, 124.2 (q, *J* = 285 Hz), 121.3, 116.2, 75.5 (q, *J* = 28 Hz), 47.5, 21.3 (q, *J* = 2.37 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.7 (d, *J* = 6.97 Hz).

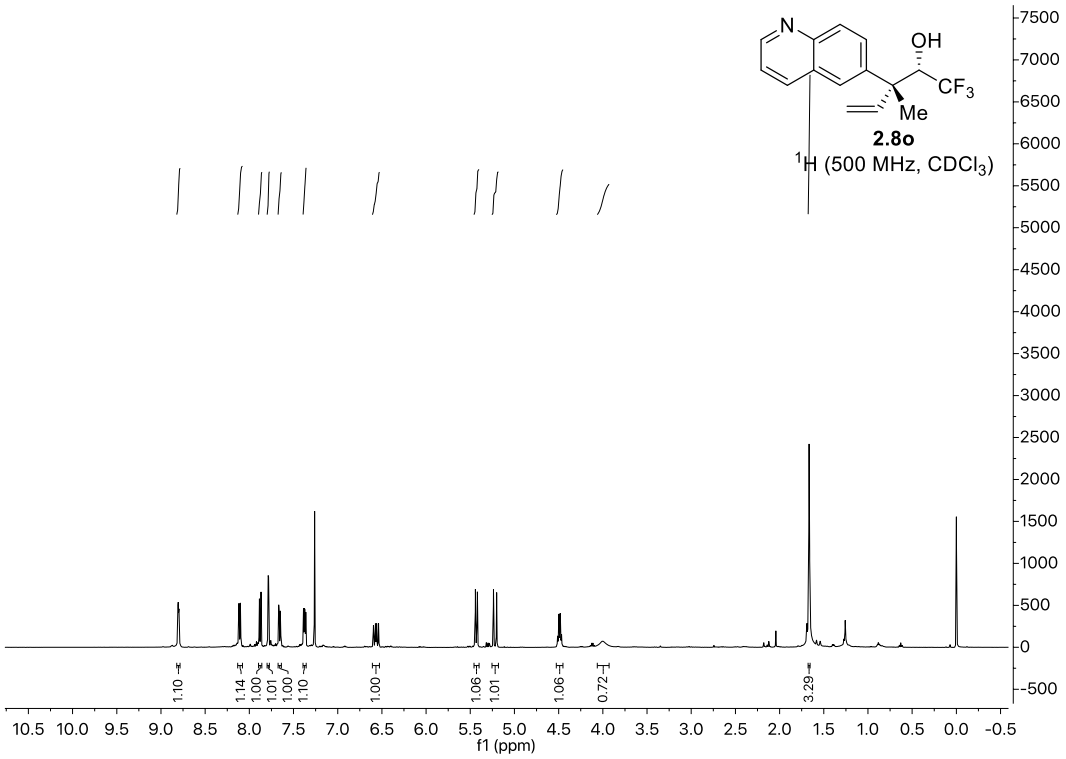
HRMS (ESI + H, *m/z*) for $C_{15}H_{14}F_3NO$: calcd. = 282.1100; found = 282.1008.

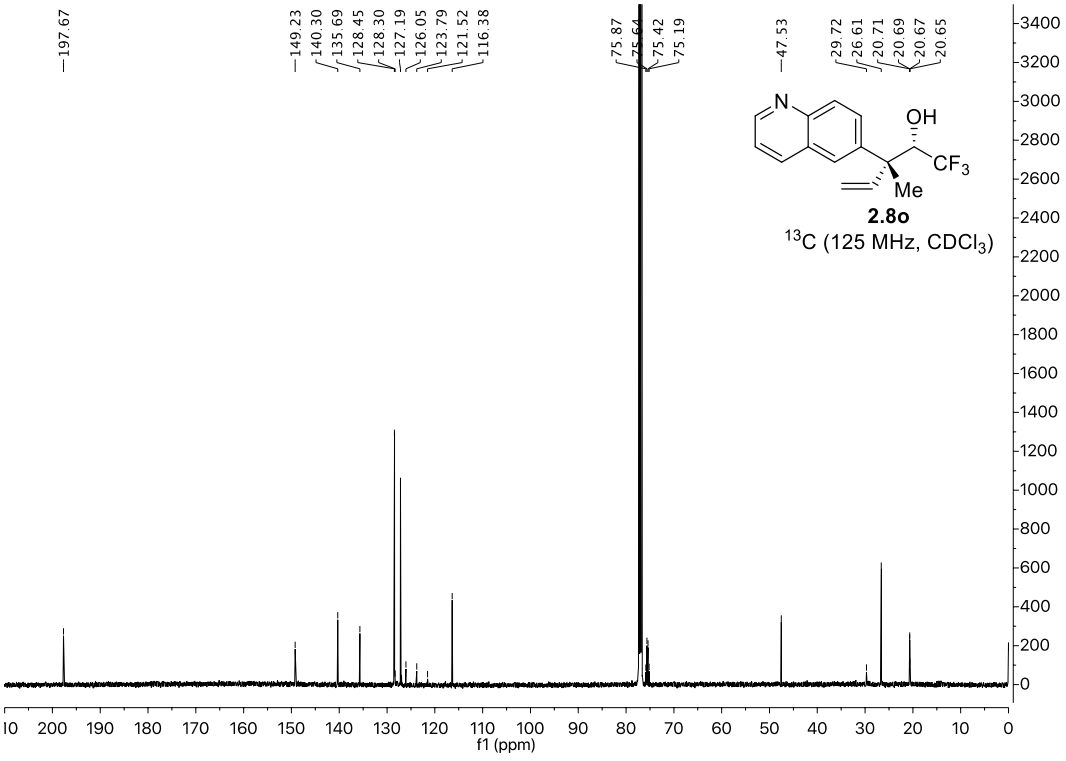
FTIR (neat): 3161, 2923, 2853, 1500, 1378, 1271, 1152, 1129, 1112, 1098, 937, 834 cm^{-1}.

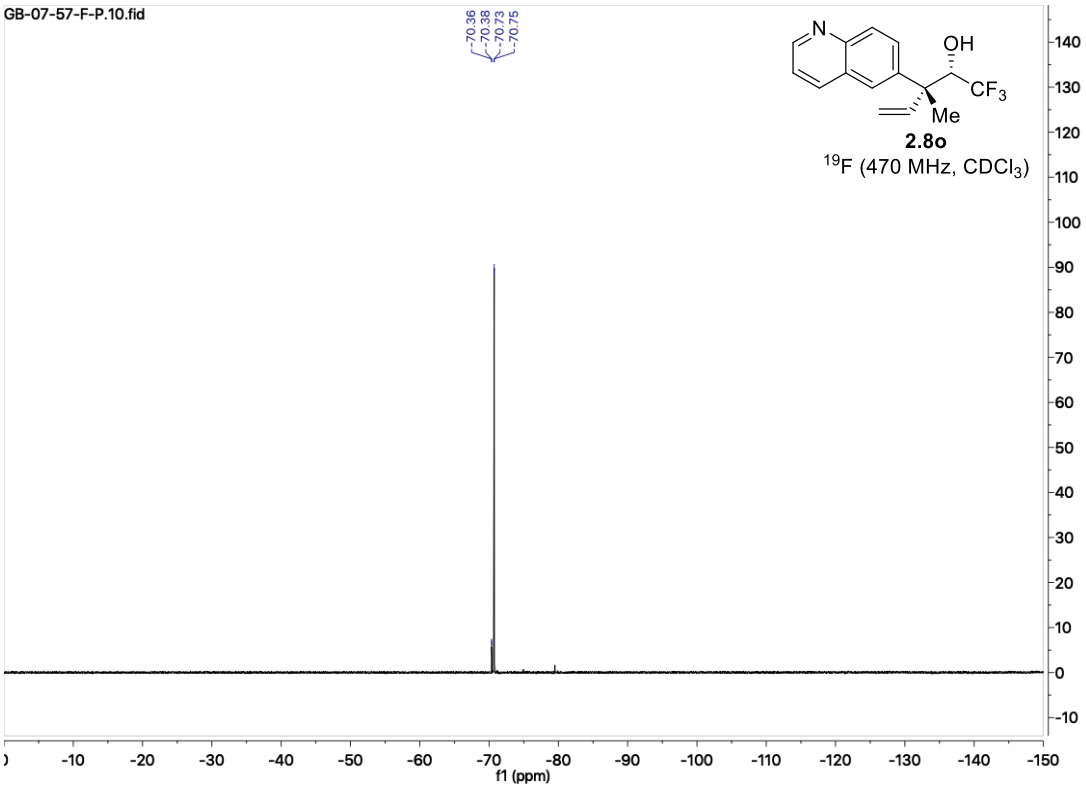
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 95%.

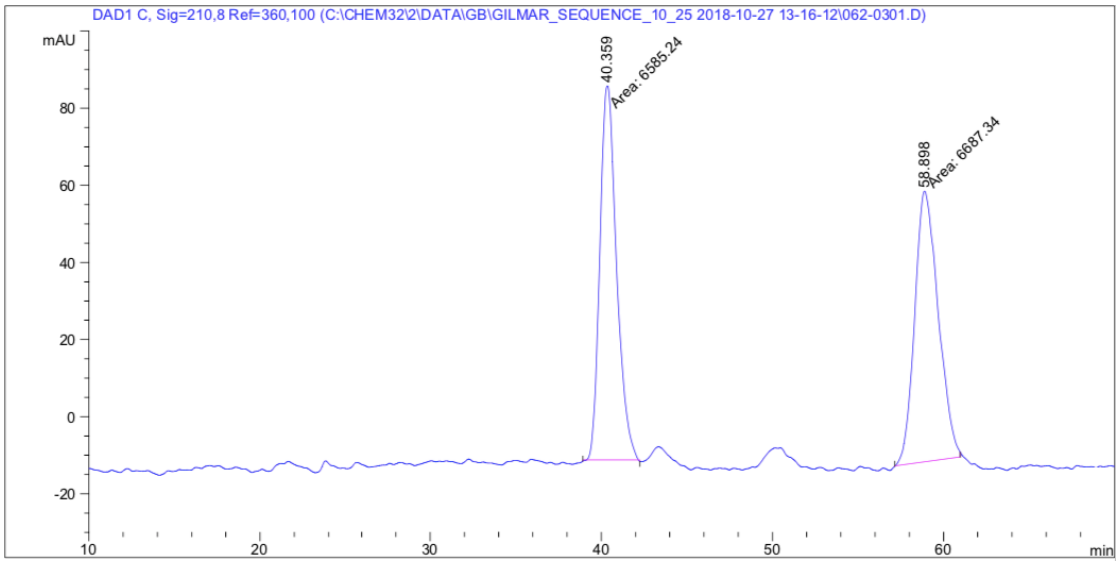
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -11.8 (c = 1.0, $CHCl_3$).

MP = 139-140 °C

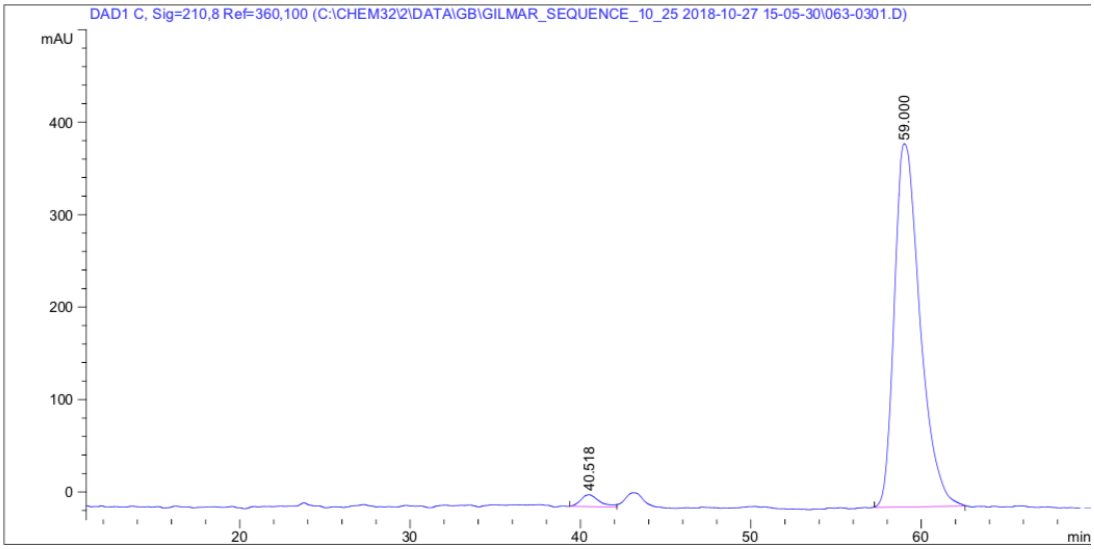

N
OH
CF3
Me
2.8o
1H (500 MHz, CDCl3)
1.10
1.14
1.00
1.01
1.00
1.10
1.00
1.06
1.01
1.06
0.72
3.29
f1 (ppm)


197.67
149.23
140.30
135.69
128.45
128.30
127.19
126.05
123.79
121.52
116.38
75.87
75.64
75.42
75.19
47.53
29.72
26.61
20.71
20.69
20.67
20.65
N
OH
CF3
Me
2.8o
13C (125 MHz, CDCl3)
f1 (ppm)


GB-07-57-F-P.10.fid
-70.36
-70.38
-70.73
-70.75
N
OH
CF3
Me
2.8o
19F (470 MHz, CDCl3)
f1 (ppm)

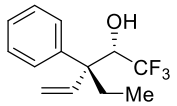


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.359	MM	1.1315	6585.24463	97.00160	49.6154
2	58.898	MM	1.5873	6687.34277	70.21903	50.3846
Totals :				1.32726e4	167.22063	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.518	BB	0.9239	982.01605	12.90356	2.3299
2	59.000	BB	1.5343	4.11656e4	392.91953	97.6701
Totals :				4.21476e4	405.82309	

(2*S*,3*R*)-3-ethyl-1,1,1-trifluoro-3-phenylpent-4-en-2-ol (2.8p)



2.8p

1,1-Disubstituted allene **2.6p** (58 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 4:96 EtOAc/hexanes), the title compound **2.8p** (37 mg, 0.15 mmol, 12:1 dr) was obtained as a yellow oil in 76% yield.

R_f = 0.41 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (m, 4H), 7.27 (m, 1H), 6.23 (dd, *J* = 10.6, 18.0 Hz, 1H), 5.47 (d, *J* = 10.6 Hz, 1H), 5.17 (d, *J* = 18.0 Hz, 1H), 4.49 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.20 (d, *J* = 7.1 Hz, 1H, O*H*), 2.04 (m, 2H), 0.68 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.6, 138.8, 128.4, 128.2, 126.9, 125.2 (q, *J* = 279 Hz), 117.6, 74.2 (q, *J* = 31 Hz), 51.9, 28.3, 8.6.

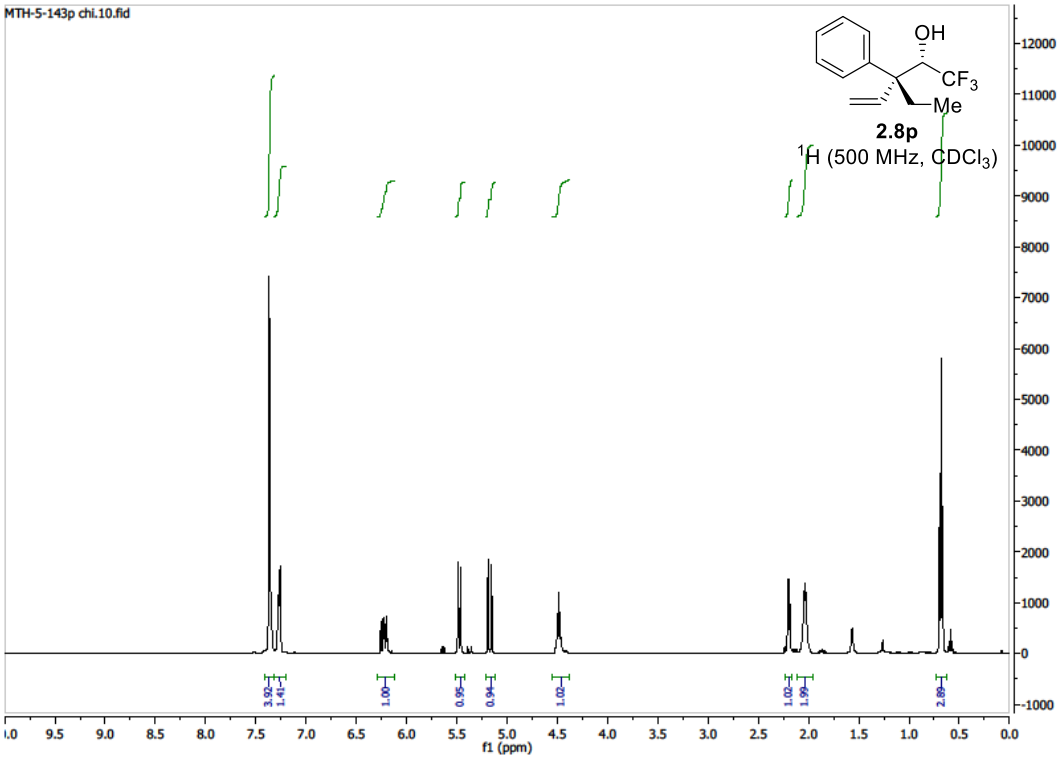
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.4 (d, *J* = 7.1 Hz).

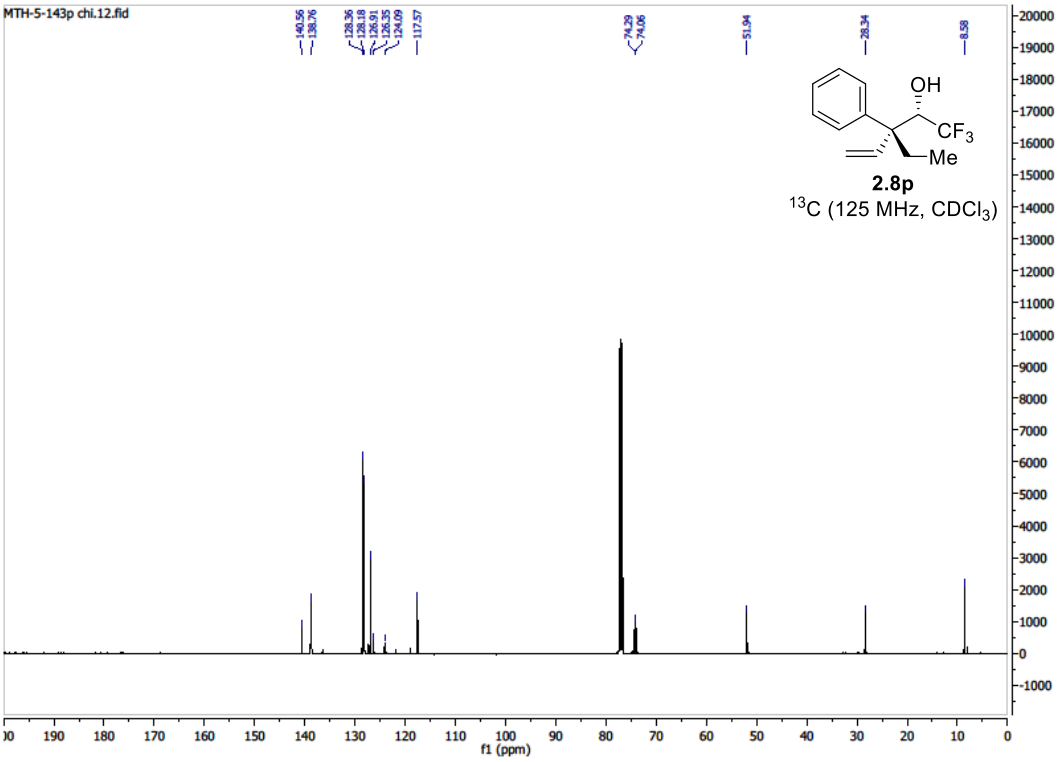
HRMS (CI+, *m/z*) for $C_{13}H_{15}OF_3$: calcd. = 244.1075; found = 244.1071.

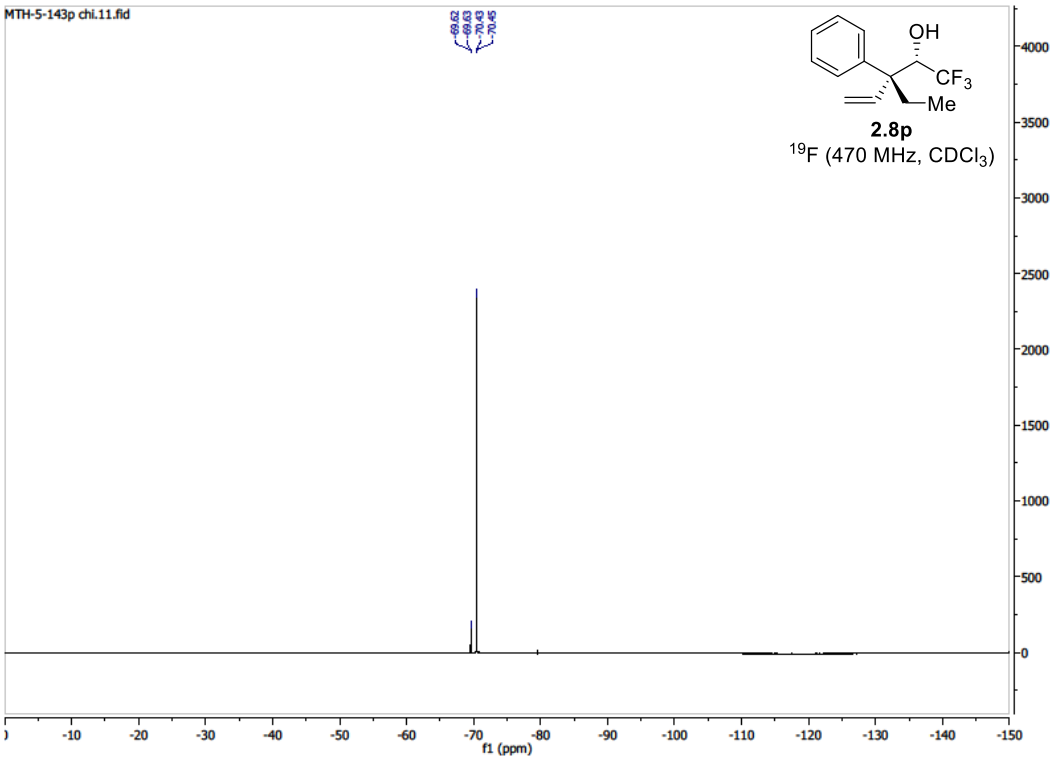
FTIR (neat): 3473, 2980, 2367, 1497, 1447, 1271, 1155, 1121, 1088, 926, 752, 701 cm^{-1}.

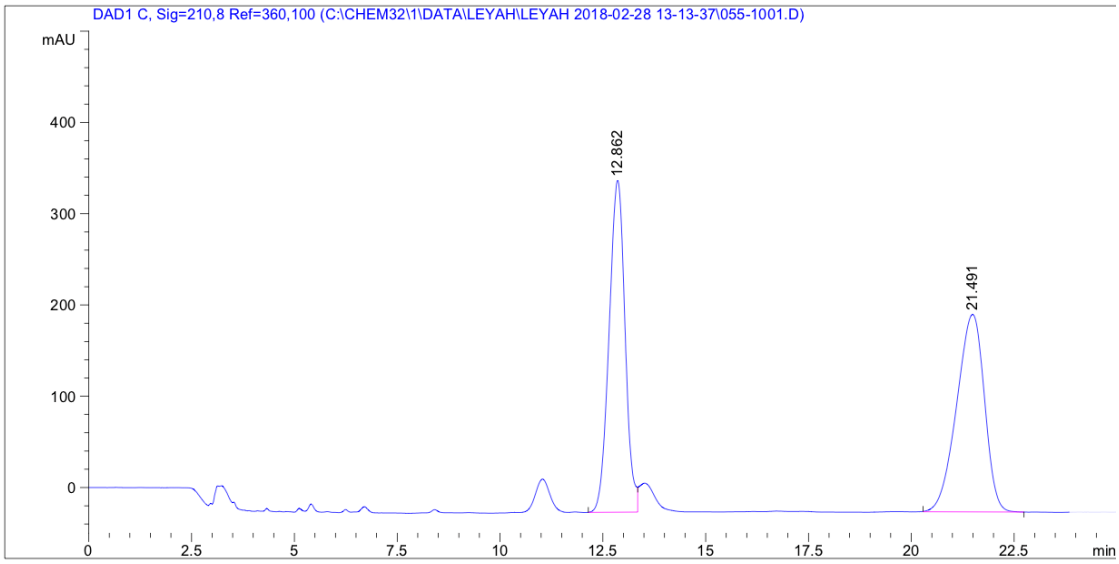
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 93%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -5.3 (c = 1.0, $CHCl_3$).

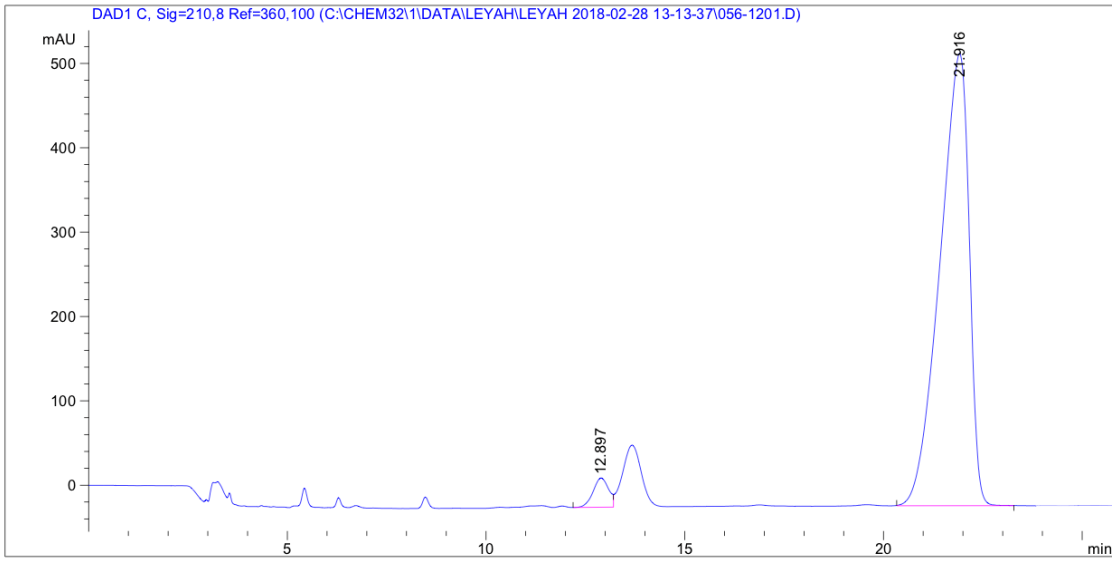

MTH-5-143p chi.10.fid
OH
CF3
Me
2.8p
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-143p chi.12.fid
OH
CF3
Me
2.8p
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-5-143p chi.11.fid
-69.62
-69.63
-70.43
-70.45
OH
CF3
Me
2.8p
19F (470 MHz, CDCl3)
4000
3500
3000
2500
2000
1500
1000
500
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

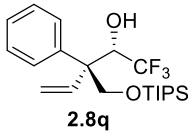


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.862	BV	0.4215	9831.89063	363.61066	49.1441
2	21.491	BB	0.7304	1.01744e4	216.43417	50.8559



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	VV	0.4133	943.10052	34.67616	3.3283
2	21.916	BB	0.7740	2.73927e4	536.21484	96.6717

(2*S*,3*R*)-1,1,1-trifluoro-3-phenyl-3-(((triisopropylsilyl)oxy)methyl)pent-4-en-2-ol (2.8q)



2.8q

1,1-Disubstituted allene **2.6q** (121 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 3:97 EtOAc/hexanes), the title compound **2.8q** (46.3 mg, 0.12 mmol, 20:1 dr) was obtained as a yellow oil in 58% yield. Note: HPLC traces were run on the silyl deprotected material.

R_f = 0.44 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.25 (m, 3H), 6.21 (dd, *J* = 10.9, 17.0 Hz, 1H), 5.41 (d, *J* = 10.9 Hz, 1H), 5.27 (d, *J* = 17.0 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.75 (d, *J* = 9.5 Hz, 1H), 4.63 (dq, *J* = 7.8, 8.5 Hz, 1H), 4.23 (d, *J* = 9.5 Hz, 1H), 1.14 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.6, 139.5, 128.3, 127.5, 127.3, 125.6 (q, *J* = 286 Hz), 117.1, 75.8 (q, *J* = 23 Hz), 69.2 (q, *J* = 2 Hz), 50.1, 18.0, 11.9.

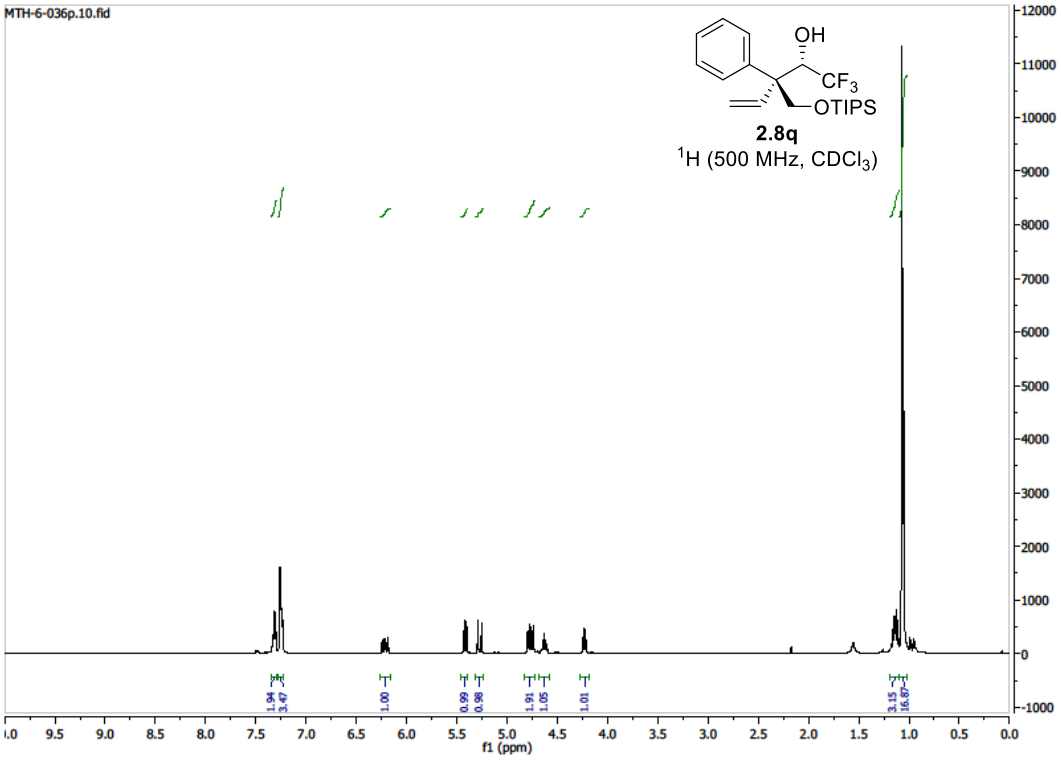
^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.2 (d, *J* = 8.0 Hz).

HRMS (ESI+Na, *m/z*) for $C_{21}H_{33}F_3O_2Si$: calcd. = 425.2094; found = 425.2091.

FTIR (neat): 3421, 2944, 2867, 2361, 1464, 1386, 1262, 1173, 1092, 882, 768 cm^{-1}.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 92:8, 1.0 mL/min, 210 nm) ee = 99%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +9.0 (c = 1.0, $CHCl_3$).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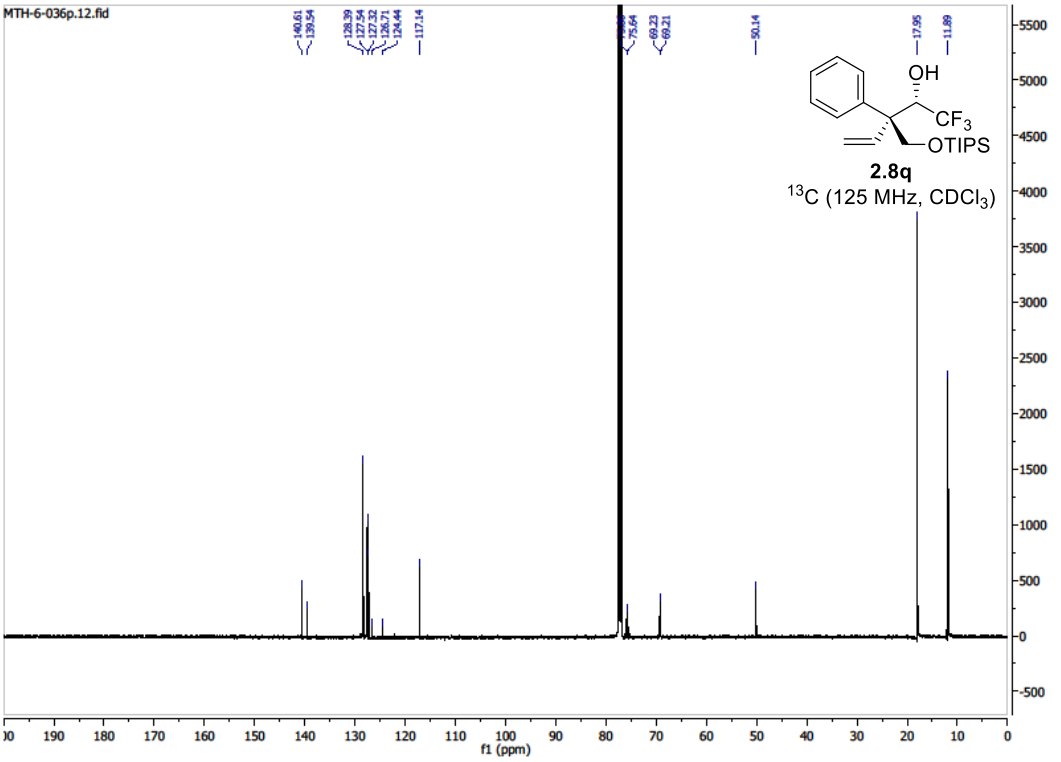
OH
CF3
OTIPS
2.8q
1H (500 MHz, CDCl3)
f1 (ppm)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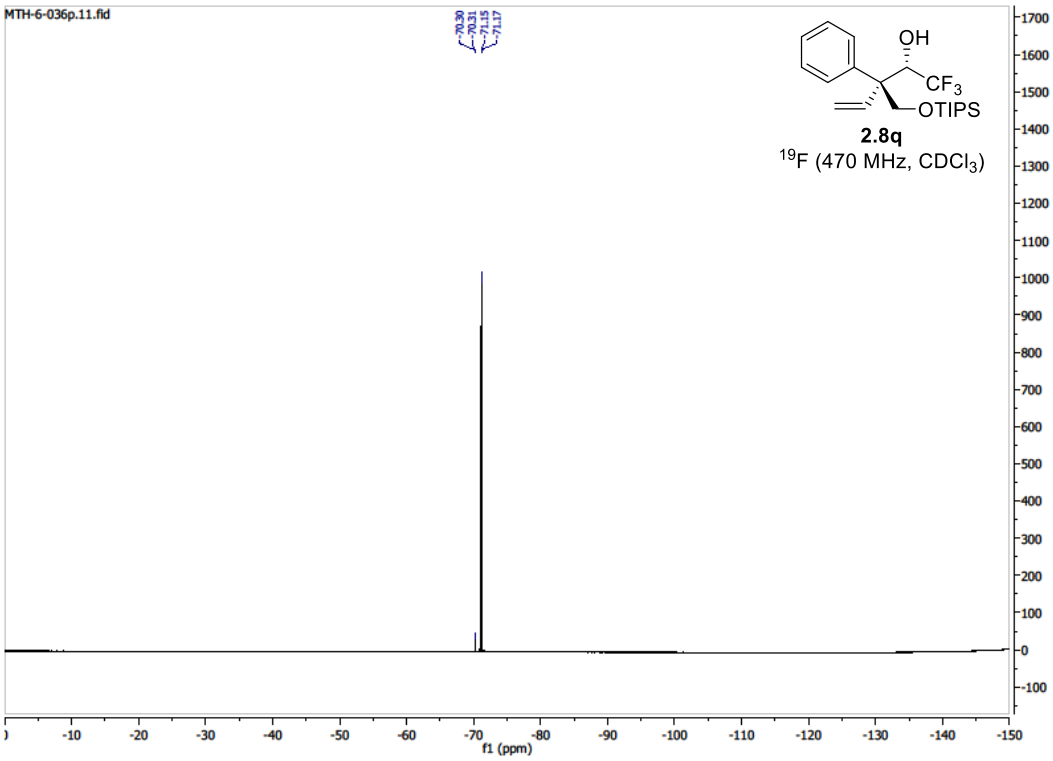
OH
CF3
OTIPS
2.8q
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-036p.11.fid
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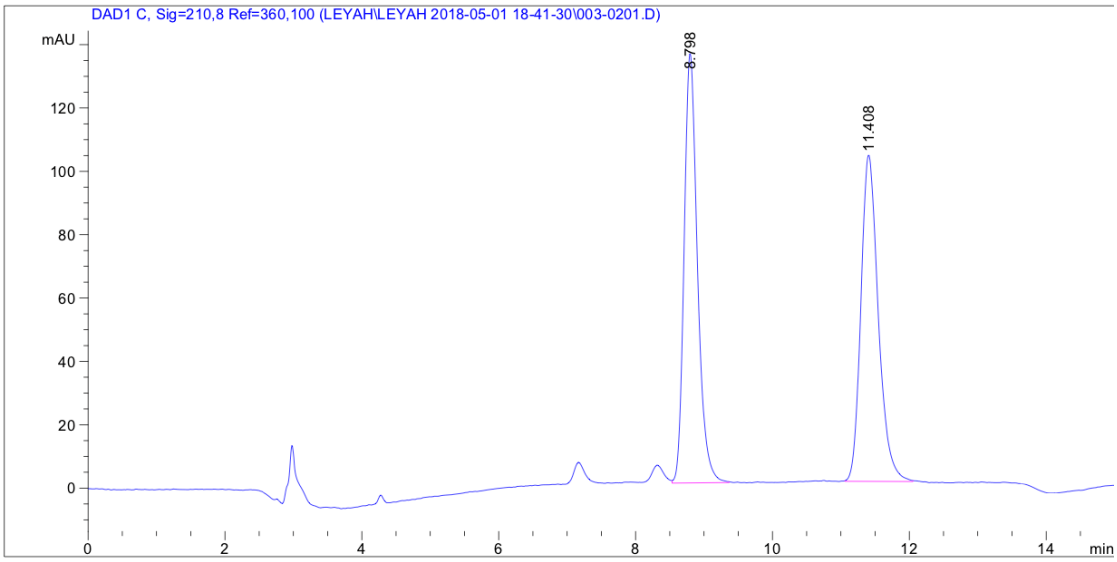
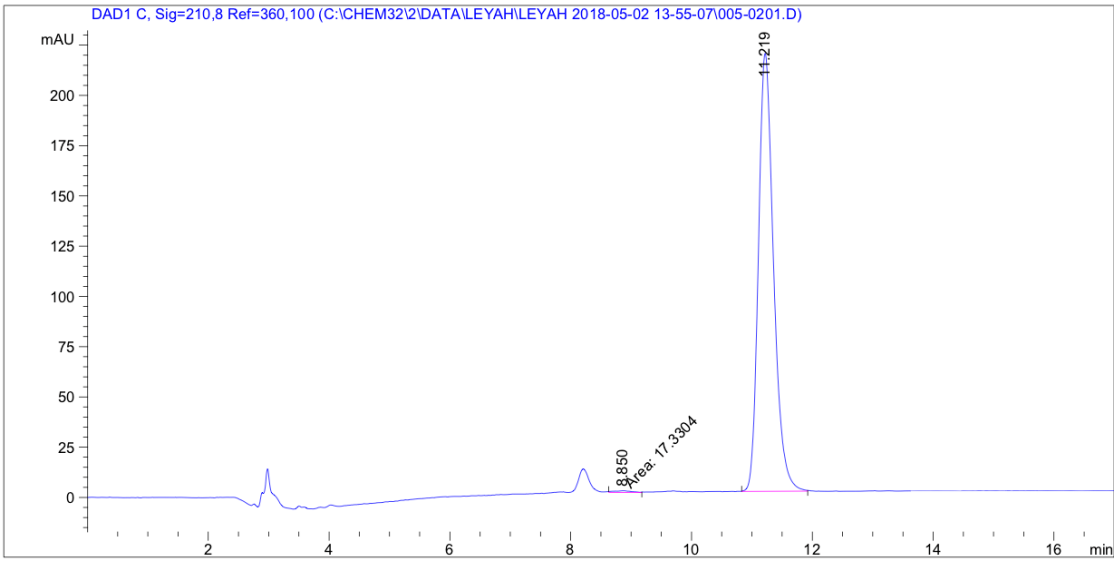
-71.15
-71.17
OH
CF3
OTIPS
2.8q
19F (470 MHz, CDCl3)
f1 (ppm)

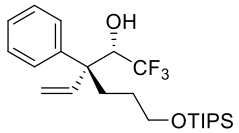


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.798	VB	0.2054	1829.16199	135.56544	50.1325
2	11.408	BB	0.2701	1819.48975	103.01164	49.8675



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.850	MM	0.3378	17.33039	8.55057e-1	0.4554
2	11.219	BB	0.2648	3788.26733	217.90428	99.5446

(2*S*,3*R*)-1,1,1-trifluoro-3-phenyl-6-((triisopropylsilyl)oxy)-3vinylhexan-2-ol (2.8r)



2.8r

1,1-Disubstituted allene **2.6r** (132 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 3:97 EtOAc/hexanes), the title compound **2.8r** (72.2 mg, 0.17 mmol, 10:1 dr) was obtained as a yellow oil in 84% yield. Note: HPLC traces were run on the silyl deprotected material.

R_f = 0.47 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.33 (m, 4H), 7.26 (m, 1H), 6.24 (dd, *J* = 11.6, 18.3 Hz, 1H), 5.46 (d, *J* = 11.6 Hz, 1H), 5.23 (d, *J* = 18.3 Hz, 1H), 4.47 (dq, *J* = 7.0, 7.0 Hz, 1H), 3.59 (m, 2H), 2.34 (d, *J* = 7.0 Hz, 1H, O*H*), 2.17-2.02 (m, 2H), 1.32 (m, 1H), 1.23 (m, 1H), 1.07-1.01 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.9, 138.7, 128.4, 128.1, 126.9, 125.2 (q, *J* = 285 Hz), 117.5, 74.8 (q, *J* = 29 Hz), 63.4, 51.2, 31.8, 27.6, 18.0, 11.9.

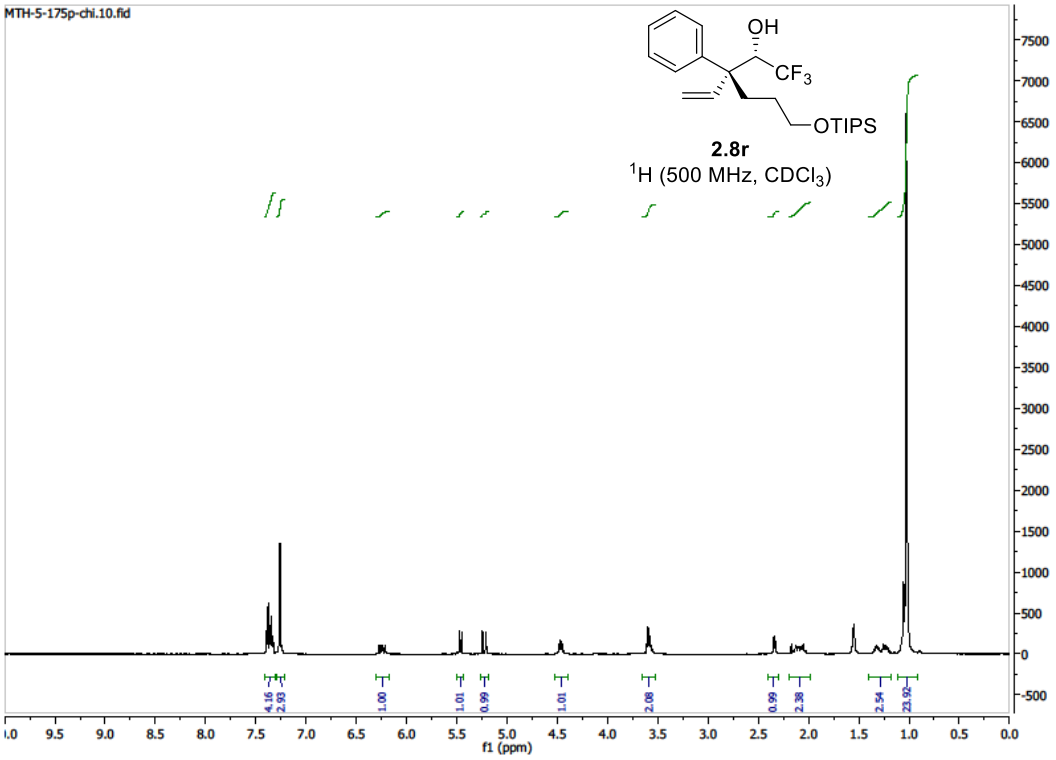
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.4 (d, *J* = 7.0 Hz).

HRMS (ESI+H, *m/z*) for $C_{23}H_{37}F_3O_2Si$: calcd. = 431.2588; found = 431.2580.

FTIR (neat): 3438, 2943, 2866, 1497, 1463, 1274, 1163, 1115, 1033, 921, 883, 701 cm^{-1}.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 92:8, 1.0 mL/min, 210 nm) ee = 95%.

$[\alpha]_D^{24}$**=** +24.5 (c = 0.51, $CHCl_3$).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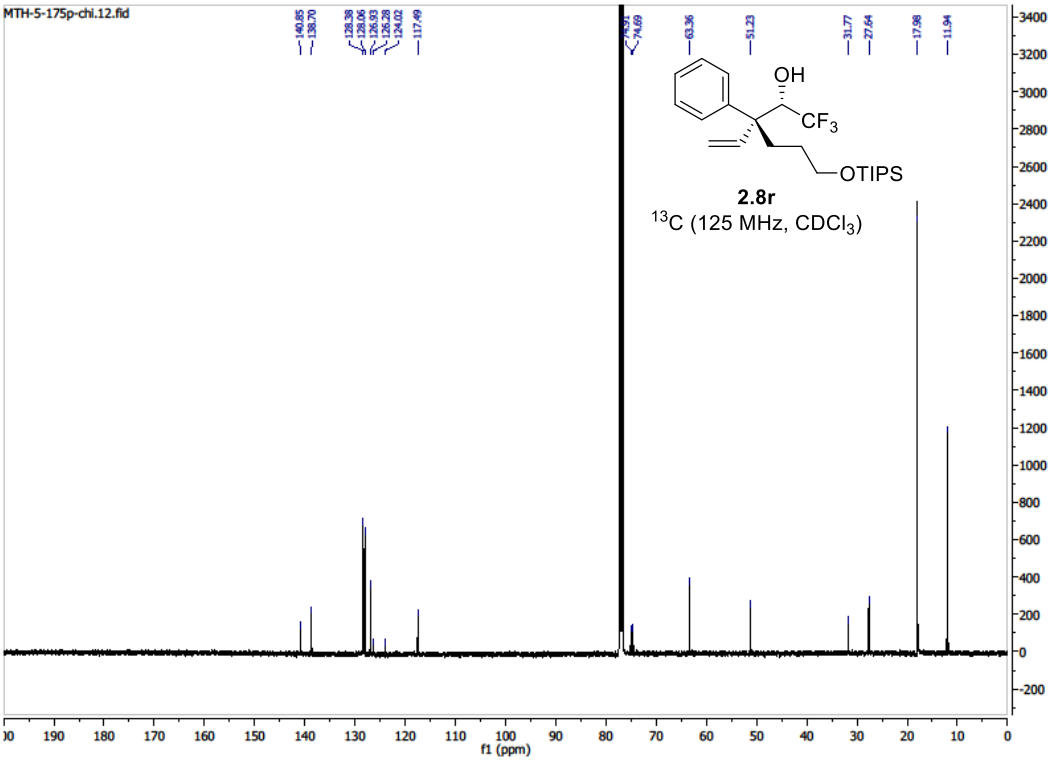
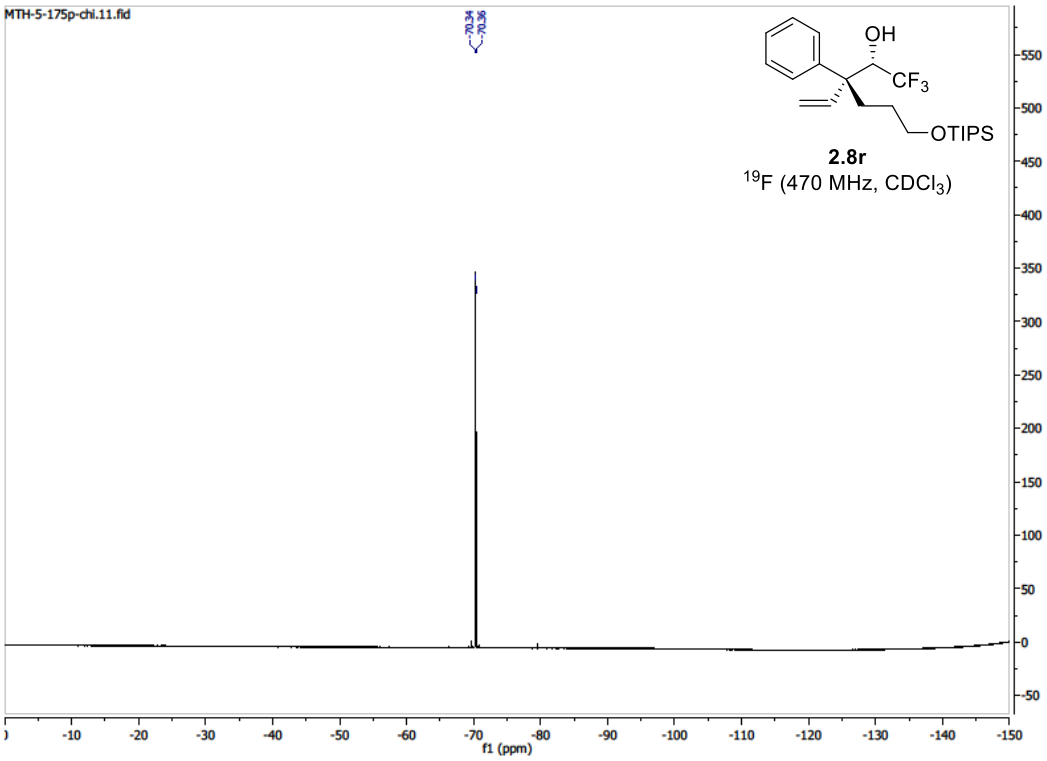
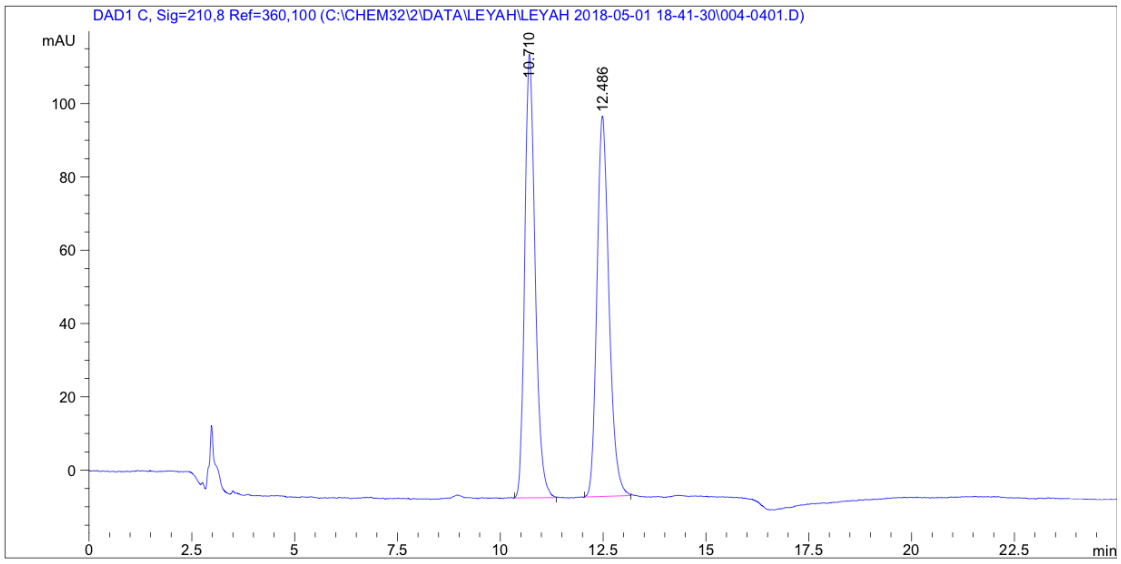
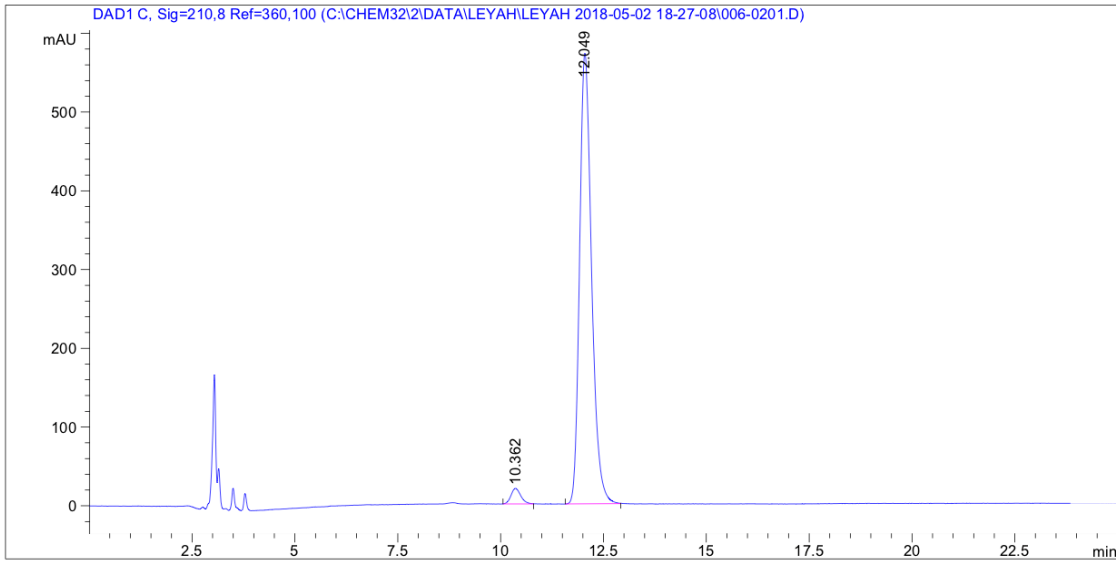
OH
CF3
OTIPS
2.8r
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-5-175p-chi.12.fid
OH
CF3
OTIPS
2.8r
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-5-175p-chi.11.fid
-70.34
-70.36
OH
CF3
OTIPS
2.8r
19F (470 MHz, CDCl3)
f1 (ppm)

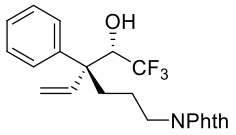


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.710	BB	0.2694	2131.26709	121.07608	50.1549
2	12.486	BB	0.3121	2118.10059	103.79050	49.8451



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.362	BB	0.2547	326.54623	19.76534	2.7443
2	12.049	BB	0.3099	1.15724e4	572.24060	97.2557

2-((*R*)-4-phenyl-4-((*S*)-2,2,2-trifluoro-2-hydroxyethyl)hex-5-en-1-yl)isoindoline-1,3-dione (2.8s)



2.8s

1,1-Disubstituted allene **2.6s** (121 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 15:85 EtOAc/hexanes), the title compound **2.8s** (65.0 mg, 0.16 mmol, 15:1 dr) was obtained as a white solid in 81% yield.

R_f = 0.37 (75:25 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (m, 2H), 7.64 (m, 2H), 7.28-7.16 (m, 5H), 6.16 (dd, *J* = 11.2, 18.2 Hz, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 5.09 (d, *J* = 18.2 Hz, 1H), 4.39 (dq, *J* = 7.2 Hz, 1H), 3.52 (t, *J* = 7.30 Hz, 2H), 2.33 (d, *J* = 7.3 Hz, 1H, O*H*), 1.98 (dd, *J* = 8.2, 9.8 Hz, 2H), 1.40 (m, 1H), 1.34 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 140.4, 138.6, 134.1, 132.1, 128.6, 128.0, 127.2, 125.2 (q, *J* = 293 Hz), 123.3, 117.8, 74.5 (q, *J* = 28 Hz), 51.3, 38.2, 32.8, 23.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.5 (d, *J* = 6.8 Hz).

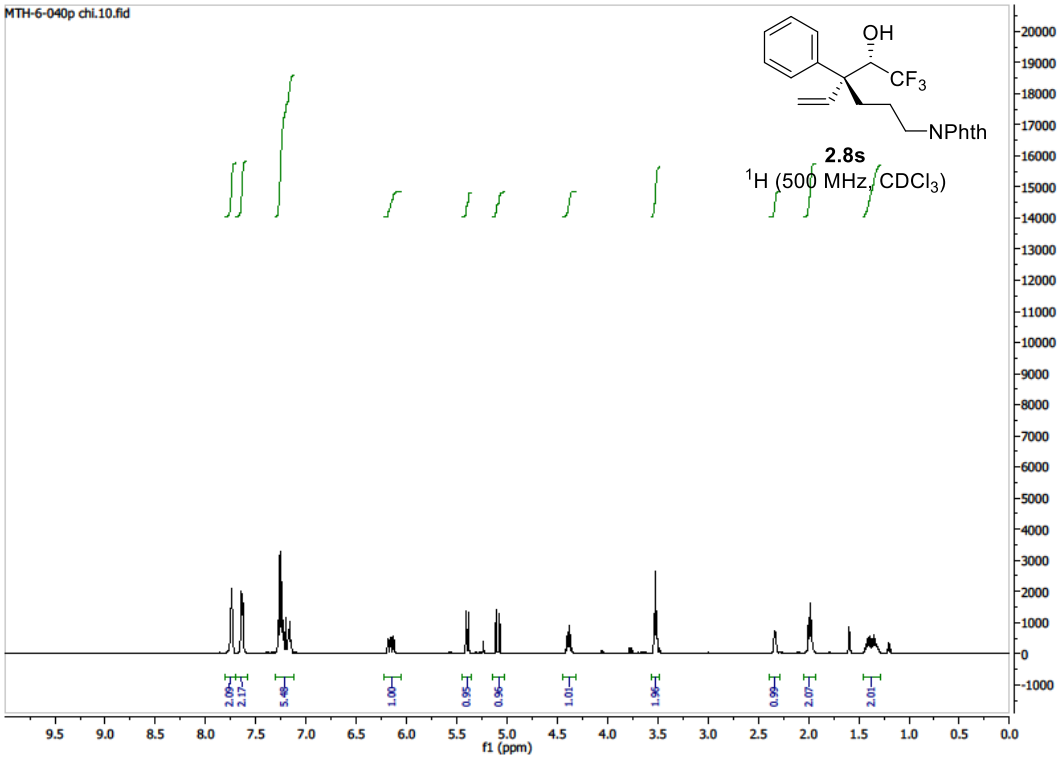
HRMS (ESI+Na, *m/z*) for $C_{22}H_{20}F_3NO_3$: calcd. = 426.1287; found = 426.1284.

FTIR (neat): 3463, 2939, 2363, 1705, 1439, 1398, 1272, 1156, 1122, 757, 721, 702 cm^{-1}.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 88:12, 1.0 mL/min, 210 nm) ee = 93%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -4.5 (c = 1.0, $CHCl_3$).

MP = 109-113 °C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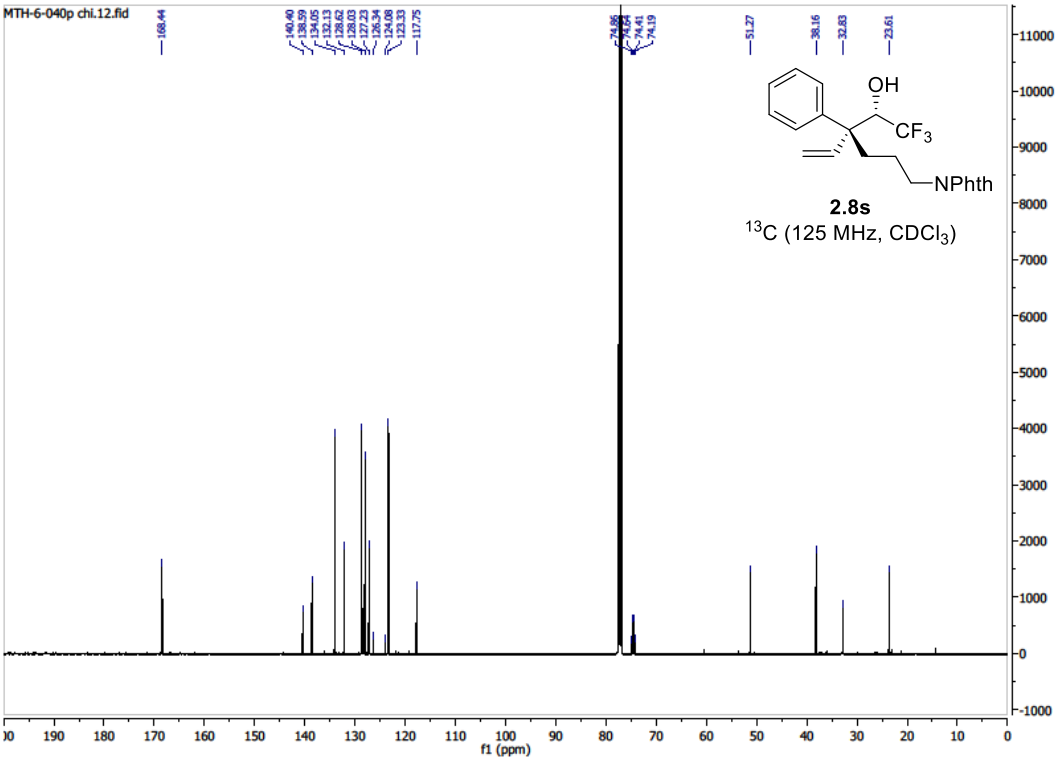
OH
CF3
NPhth
2.8s
1H (500 MHz, CDCl3)
f1 (ppm)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CF3
NPhth
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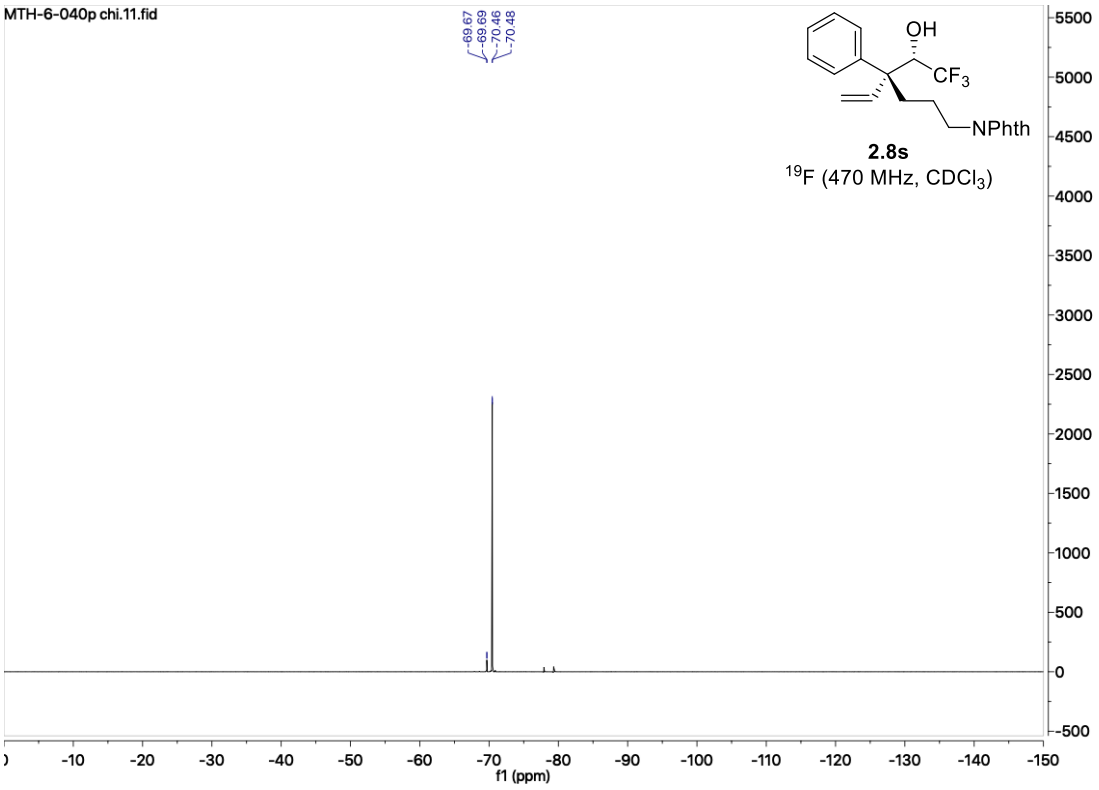
13C (125 MHz, CDCl3)
f1 (ppm)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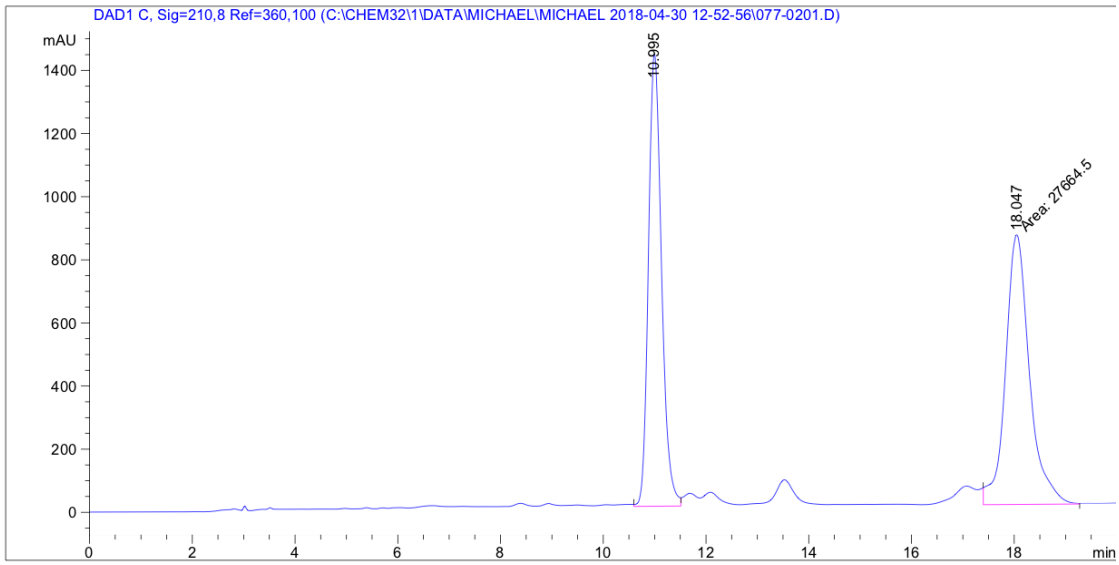
OH
CF3
NPhth
2.8s
19F (470 MHz, CDCl3)
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)



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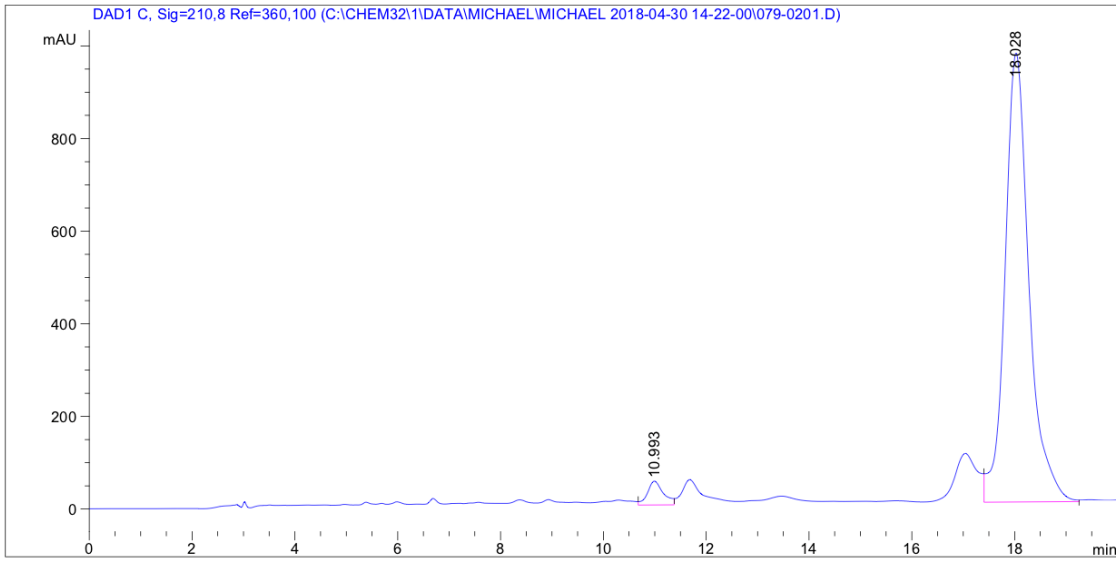
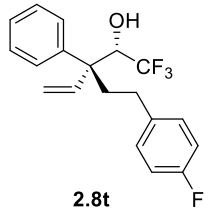
1	10.995	VV	0.2746	2.53625e4	1432.00134	47.8294
2	18.047	FM	0.5392	2.76645e4	855.16876	52.1706



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.993	VV	0.3150	1105.99231	51.41473	3.4004
2	18.028	VV	0.4901	3.14191e4	969.37616	96.5996

(2*S*,3*R*)-1,1,1-trifluoro-3-(4-fluorophenethyl)-3-phenylpent-4-en-2-ol (2.8t)



2.8t

1,1-Disubstituted allene **2.6t** (95 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 3:97 EtOAc/hexanes), the title compound **2.8t** (48.6 mg, 14 mmol, 11:1 dr) was obtained as a yellow oil in 72% yield.

R_f =0.46 (9:1 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44-7.39 (m, 4H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.00 (dd, *J* = 5.8, 8.4 Hz, 2H), 6.92 (dd, *J* = 8.4, 8.4 Hz, 2H), 6.30 (dd, *J* = 11.3, 18.3 Hz, 1H), 5.53 (d, *J* = 11.3 Hz, 1H), 5.23 (d, *J* = 18.3 Hz, 1H), 4.56 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.34-2.22 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.3 (d, *J* = 245 Hz), 140.5, 138.7, 137.6 (d, *J* = 3 Hz), 129.5 (d, *J* = 8 Hz), 128.6, 128.0, 127.2, 125.1 (q, *J* = 282 Hz), 117.9, 115.1 (d, *J* = 22 Hz), 74.3 (q, *J* = 29 Hz), 51.6, 38.2, 29.7.

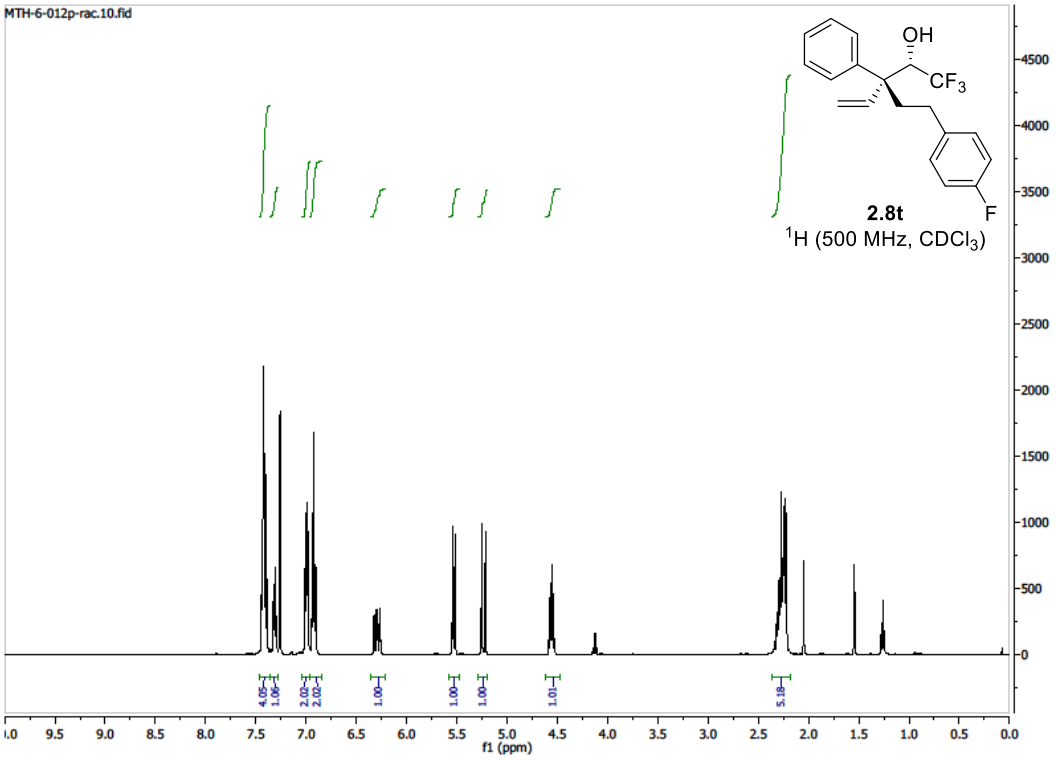
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.4 (d, *J* = 7.2 Hz), -117.5 (tt, *J* = 5.5, 8.2 Hz).

HRMS (CI+, *m/z*) for $C_{19}H_{18}OF_4$: calcd. = 338.1294; found = 338.1297.

FTIR (neat): 3459, 2993, 2363, 1496, 1416, 1271, 1156, 1122, 1018, 926, 762, 701 cm^{-1}.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -6.7 (c = 1.0, $CHCl_3$).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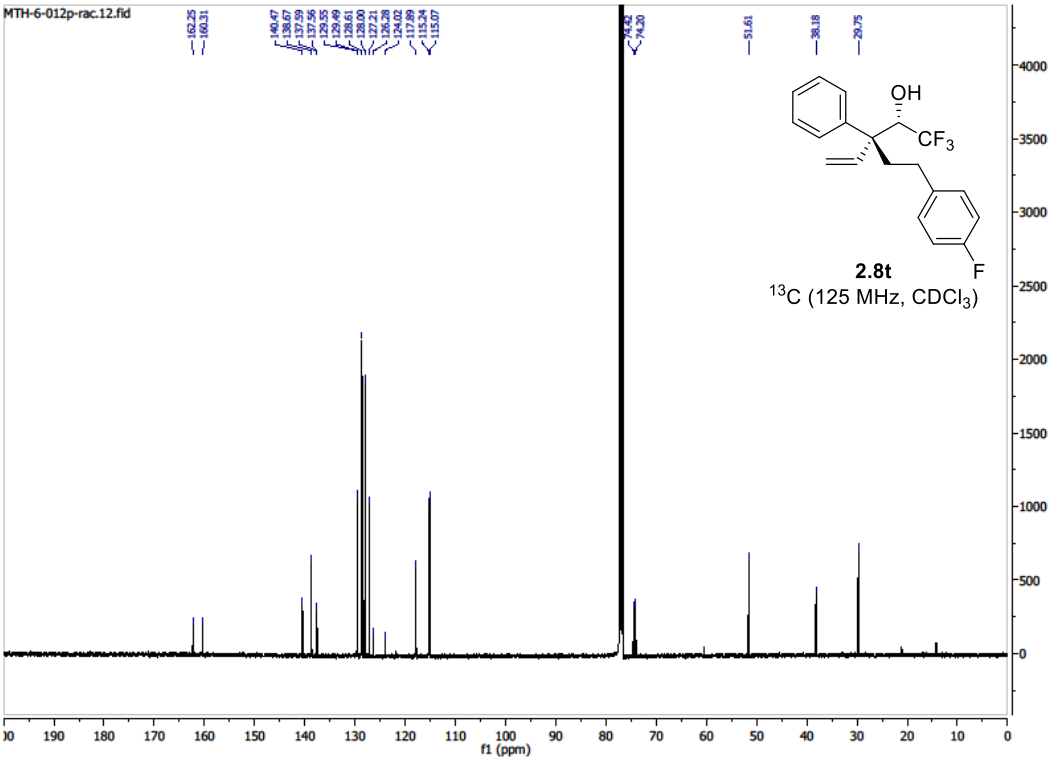
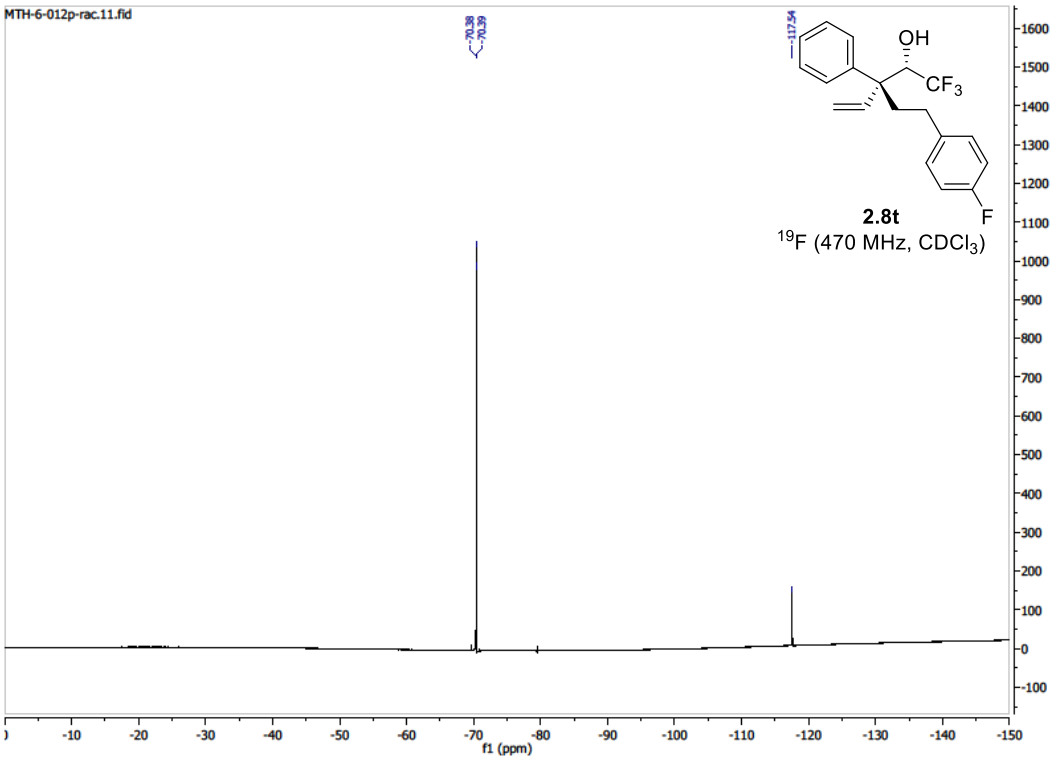
OH
CF3
F
2.8t
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-012p-rac.12.fid
OH
CF3
F
2.8t
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-012p-rac.11.fid
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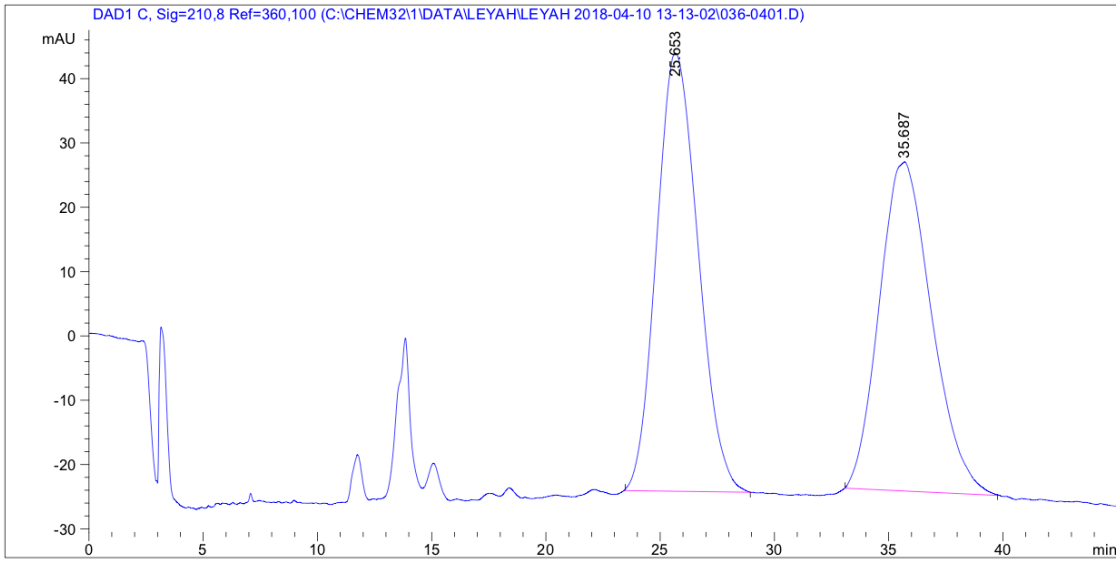
OH
CF3
F
2.8t
19F (470 MHz, CDCl3)
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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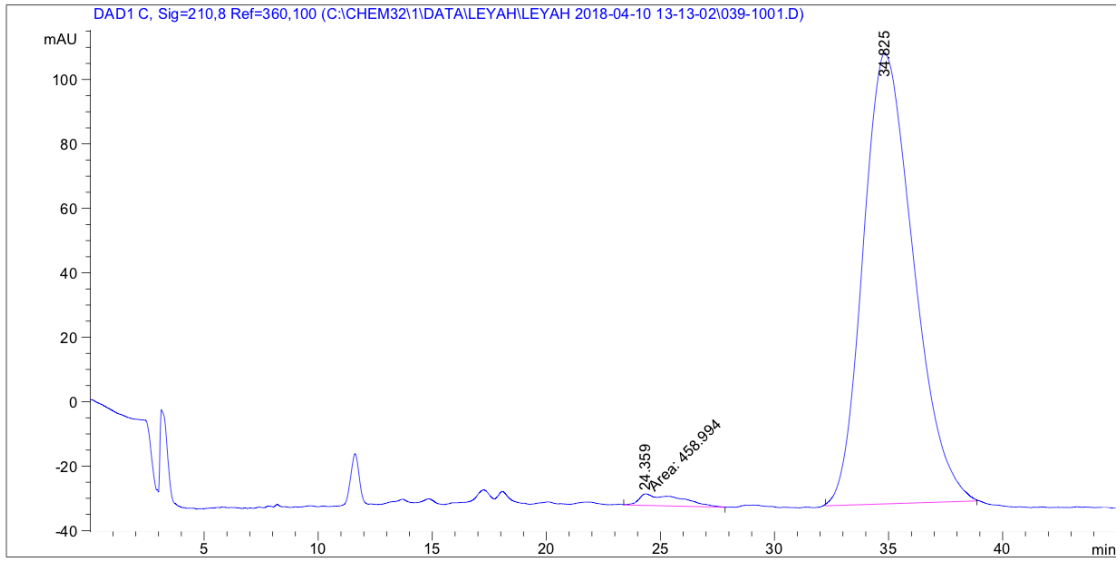
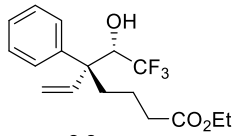
2	35.687	BB	1.8706	8144.16846	51.17627	48.6344



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.359	MM	2.1284	458.99420	3.59423	2.0944
2	34.825	BB	1.8826	2.14562e4	139.95313	97.9056

Ethyl (R)-5-phenyl-5-((S)-2,2,2-trifluoro-1-hydroxyethyl)hept-6-enoate (2.8u)



2.8u

1,1-Disubstituted allene **2.6u** (92 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 8:92 EtOAc/hexanes), the title compound **2.8u** (42.9 mg, 0.13 mmol, 9:1 dr) was obtained as a yellow oil in 65% yield.

R_f = 0.21 (85:15 hexanes : EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 4H), 7.27 (m, 1H), 6.23 (dd, *J* = 11.3, 18.2 Hz, 1H), 5.48 (d, *J* = 11.3 Hz, 1H), 5.21 (d, *J* = 18.2 Hz, 1H), 4.48 (dq, *J* = 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.40 (d, *J* = 7.3 Hz, 1H, O*H*), 2.23 (m, 2H), 2.00 (m, 2H), 1.41 (m, 1H), 1.32 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4, 140.5, 138.6, 128.5, 128.0, 127.1, 125.1 (q, *J* = 282 Hz), 117.5, 74.5 (q, *J* = 29 Hz), 60.4, 51.3, 35.0, 34.3, 19.6, 14.2.

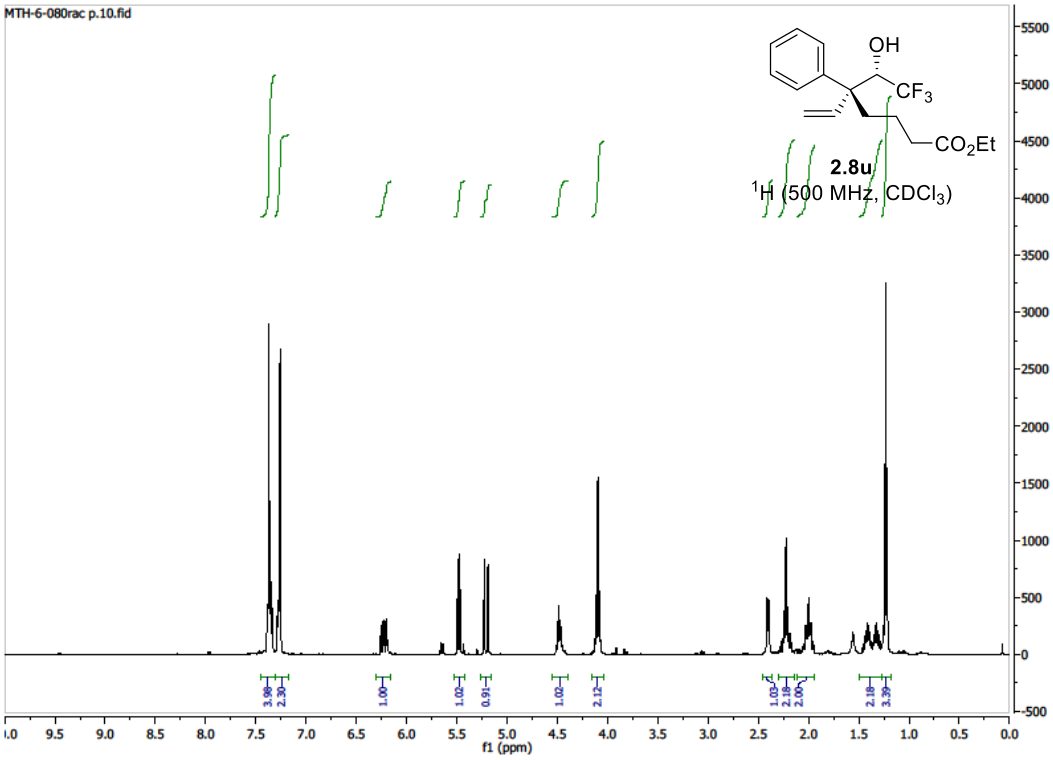
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.4 (d, *J* = 7.3 Hz).

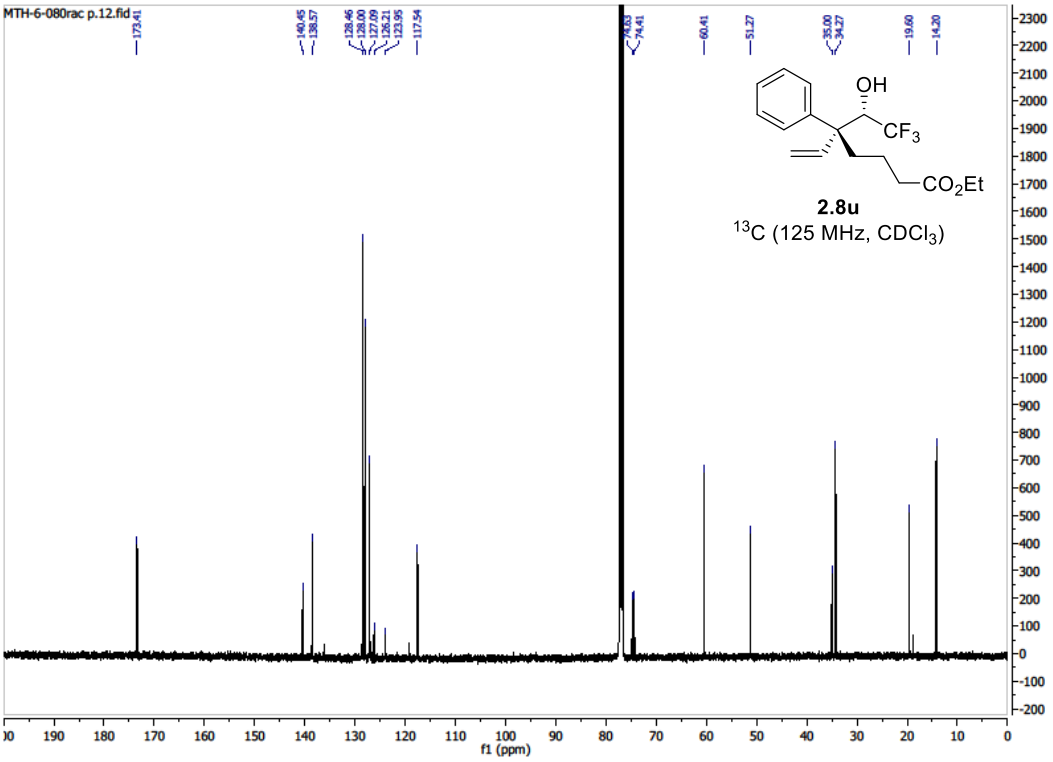
HRMS (ESI+Na, *m/z*) for $C_{17}H_{21}F_3O_3$: calcd. = 353.1335; found = 353.1336.

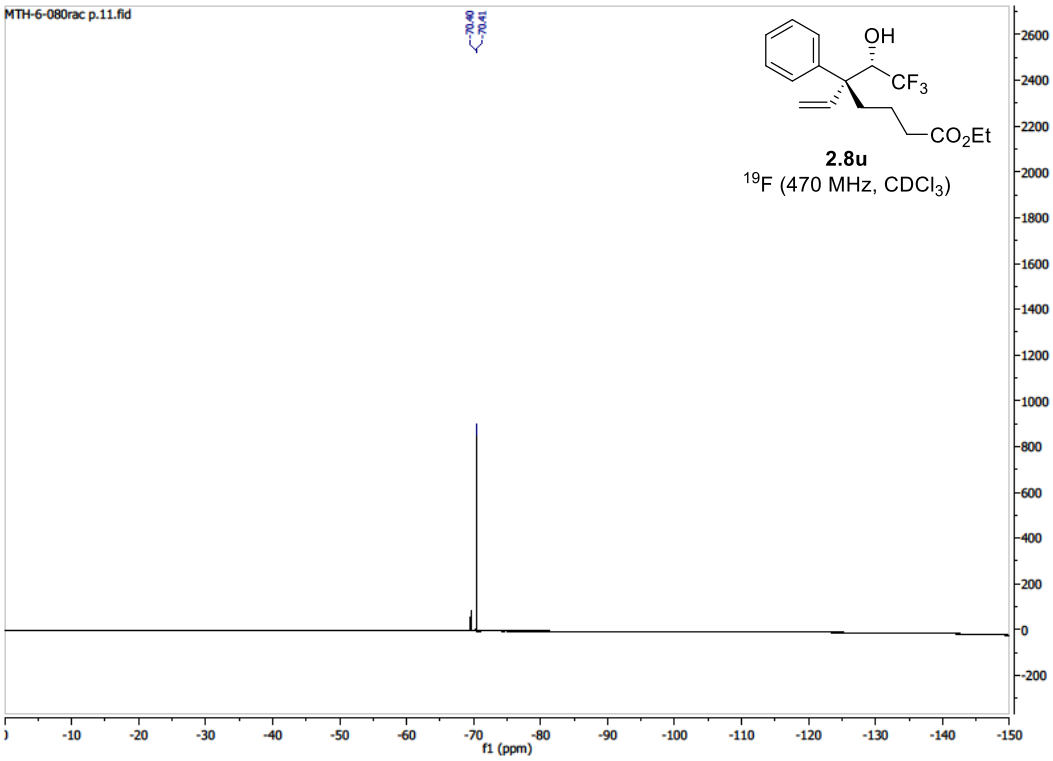
FTIR (neat): 3437, 2981, 2947, 1731, 1600, 1448, 1264, 1156, 1121, 702 cm^{-1}.

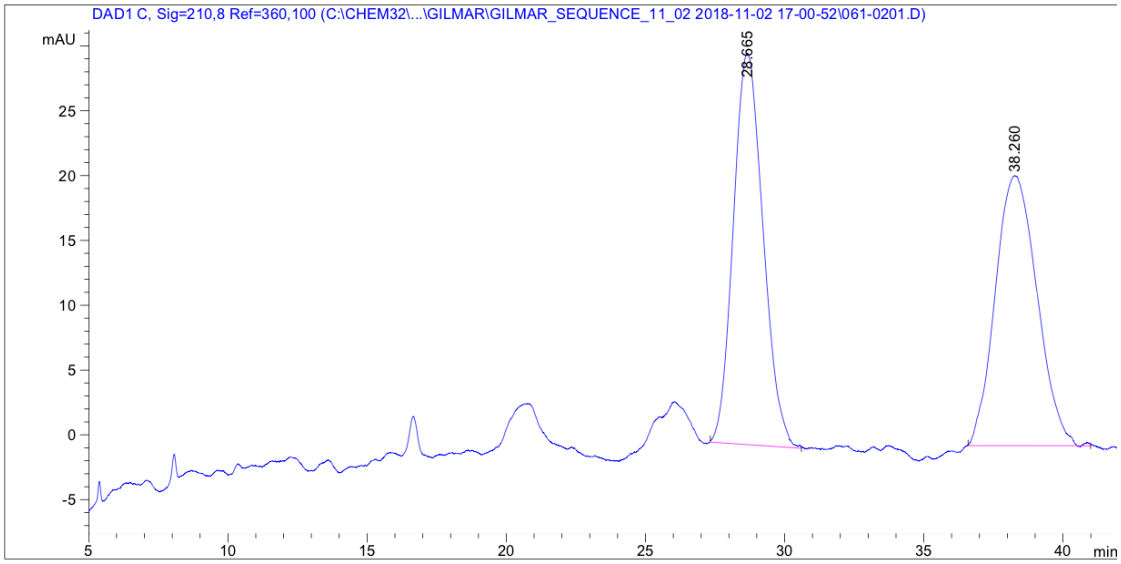
HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 210 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +10.3 (c = 0.94, $CHCl_3$).

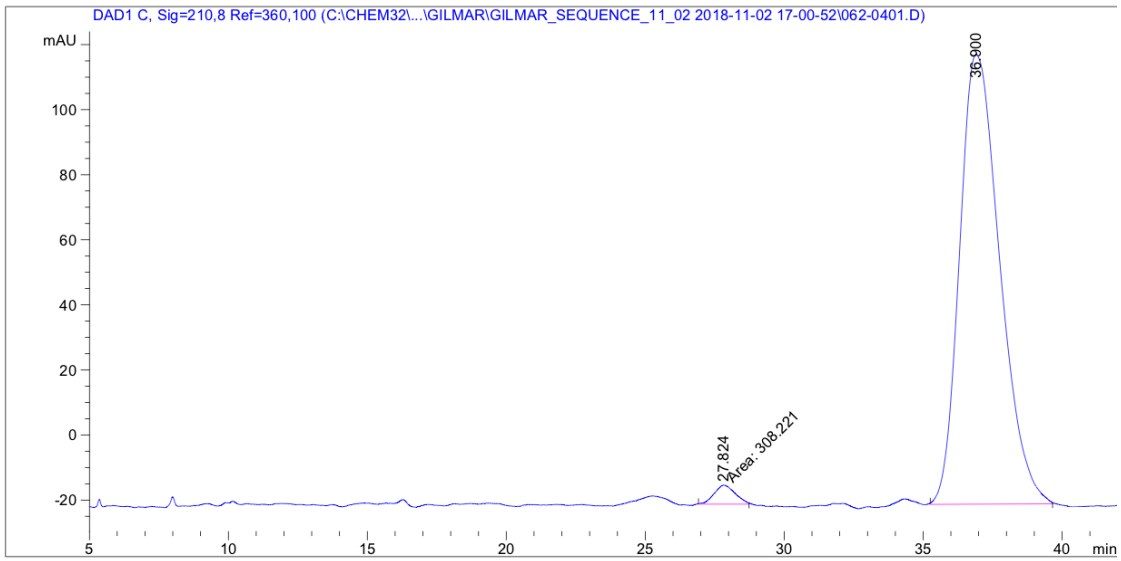

MTH-6-080rac p.10.fid
OH
CF3
CO2Et
2.8u
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-080rac p.12.fid
OH
CF3
CO2Et
2.8u
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-080rac p.11.fid
-70.40
-70.41
OH
CF3
CO2Et
2.8u
19F (470 MHz, CDCl3)
f1 (ppm)



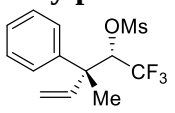
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.665	BB	0.8835	2239.67212	30.18985	50.7772
2	38.260	BB	1.2229	2171.11304	20.81524	49.2228



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.824	MM	0.8764	308.22104	5.86145	2.1695
2	36.900	BB	1.3150	1.38986e4	138.23550	97.8305

2.5.4.4 Procedures and Spectral Data for the Elaboration of Adduct 2.8a

(2*S*,3*R*)-1,1,1-trifluoro-3-methyl-3-phenylpent-4-en-2-yl methanesulfonate (2.21a)



2.21a

To a stirred solution of alcohol **2.8a** (236 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.20 mL, 1.55 mmol) followed by methanesulfonyl chloride (0.096 mL, 1.23 mmol). The reaction mixture was stirred for 14 hours at room temperature. Saturated aqueous ammonium chloride (10 mL) was added and the phases were separated. The organic phase was washed with water (2 x 10 mL). The combined aqueous phases were washed with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 96:4 hexanes:ethyl acetate) to afford the title compound **2.21a** (276 mg, 0.89 mmol) as a colorless oil in 87% yield. Note: the starting material and product have identical R_f values so TLC is not an appropriate method for determining reaction completion.

R_f = 0.41 (9:1 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 8.9 Hz, 2H), 7.37 (dd, *J* = 8.9, 8.9 Hz, 2H), 7.28 (t, *J* = 8.9 Hz, 1H), 6.42 (dd, *J* = 10.8, 17.4 Hz, 1H), 5.42 (d, *J* = 10.8 Hz, 1H), 5.33 (q, *J* = 6.9 Hz, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 2.53 (s, 3H), 1.63 (s, 3H).

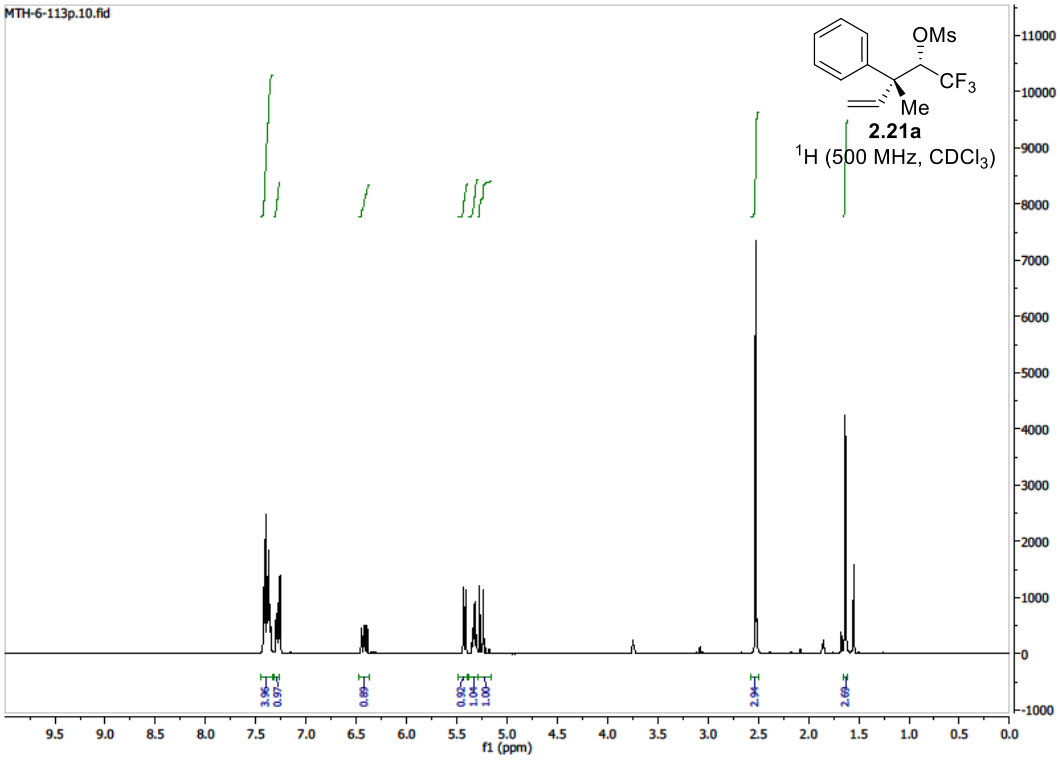
^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.2, 139.1, 128.8, 127.6, 127.0, 123.3 (q, *J* = 284 Hz), 116.6, 82.8 (q, *J* = 30 Hz), 46.7, 38.9, 20.9.

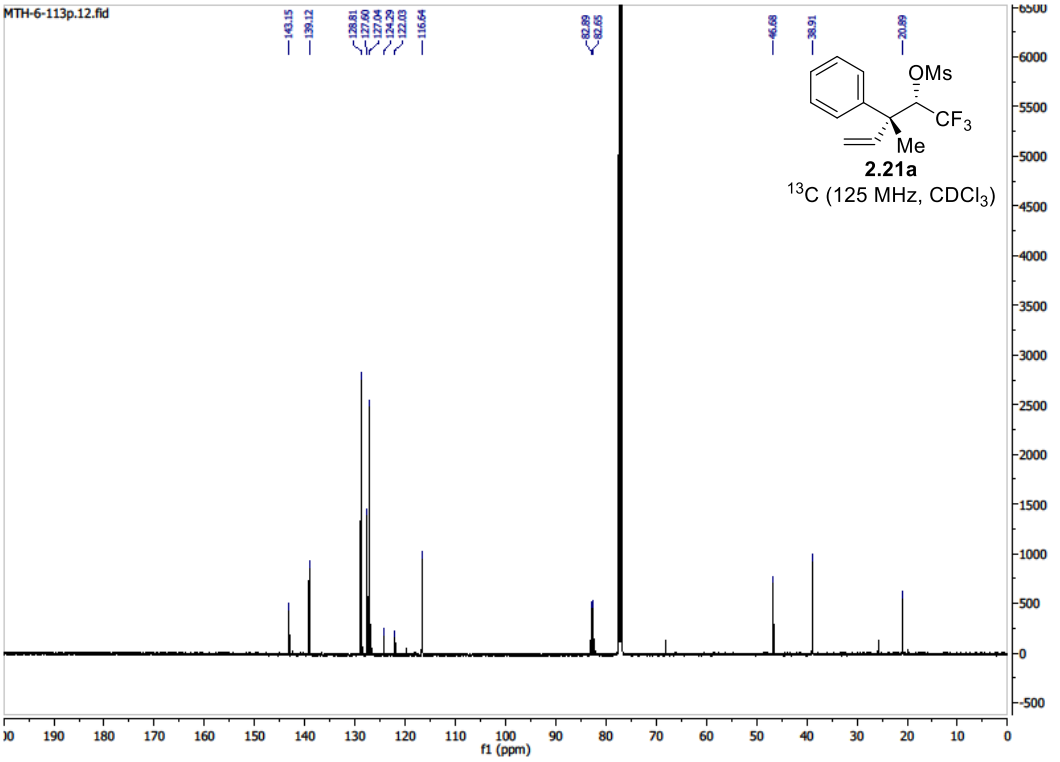
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.6 (d, *J* = 6.9 Hz).

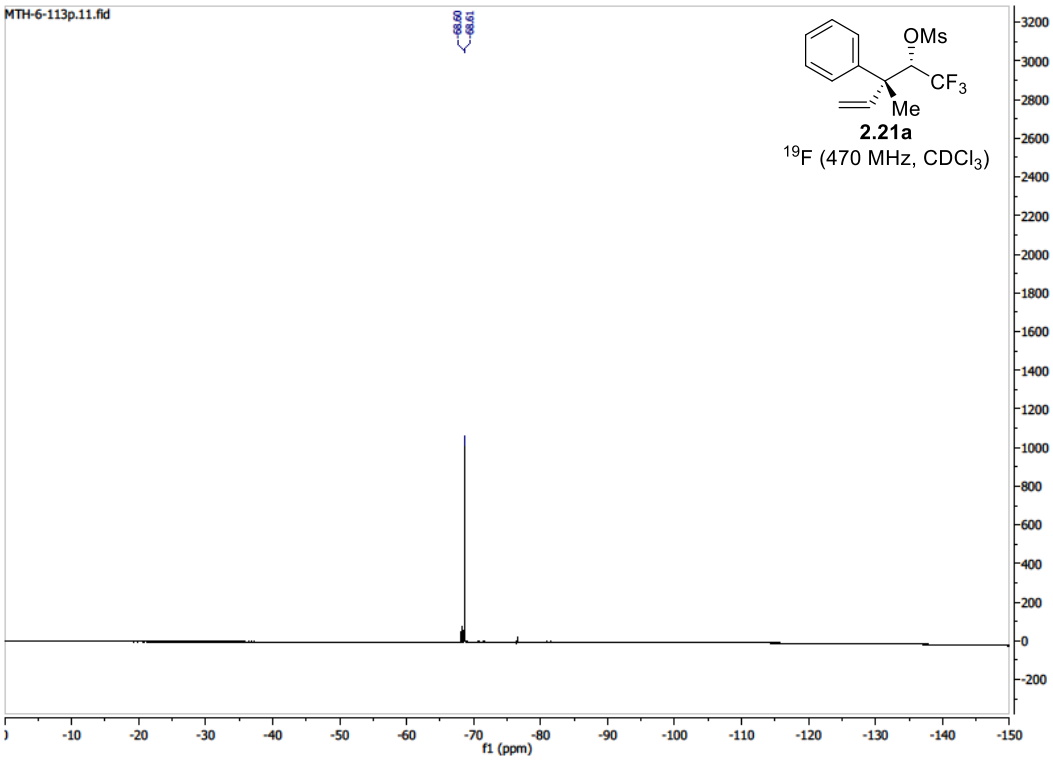
HRMS (ESI+Na, *m/z*) for $C_{13}H_{15}F_3O_3S$: calcd. = 331.0586; found = 331.0589.

FTIR (neat): 2982, 1497, 1361, 1275, 1176, 1016, 964, 793 cm^{-1}.

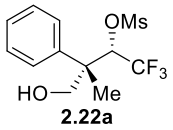
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +8.0 (c = 0.93, $CHCl_3$).


MTH-6-113p.10.fid
OMs
CF3
Me
2.21a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-113p.12.fid
143.15
139.12
128.81
127.60
127.04
124.29
122.03
116.64
82.89
82.65
46.68
38.91
20.89
OMs
CF3
Me
2.21a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-113p.11.fid
-68.60
-68.61
OMs
CF3
Me
2.21a
19F (470 MHz, CDCl3)
f1 (ppm)

(2*S*,3*S*)-1,1,1-trifluoro-4-hydroxy-3-methyl-3-phenylbutan-2-yl methanesulfonate (2.22a)



2.22a

To a stirred flask containing mesylate **2.21a** (154 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added MeOH (1 mL) and the reaction mixture was cooled to -78 °C. Ozone was bubbled through the solution until the solution turned blue (~5 mins). N_2 was bubbled through the solution to remove the excess ozone. $NaBH_4$ (85 mg, 2.5 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 14 hours. Saturated aqueous ammonium chloride (5 mL) was added and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (2 x 5 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 75:25 hexanes:ethyl acetate) to afford the title compound **2.22a** (136 mg, 0.44 mmol) as a colorless oil in 87% yield.

R_f = 0.23 (80:20 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 7.8 Hz, 2H), 7.39 (dd, *J* = 7.7, 8.4 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 5.61 (q, *J* =7.4 Hz, 1H), 3.95 (dd, *J* = 6.1, 11.5 Hz, 1H), 3.60 (dd, *J* = 7.1. 11.5 Hz, 1H), 3.17 (s, 3H), 1.96 (t, *J* = 6.5 Hz, 1H, O*H*), 1.50 (q, *J* = 1.2 Hz, 3H).

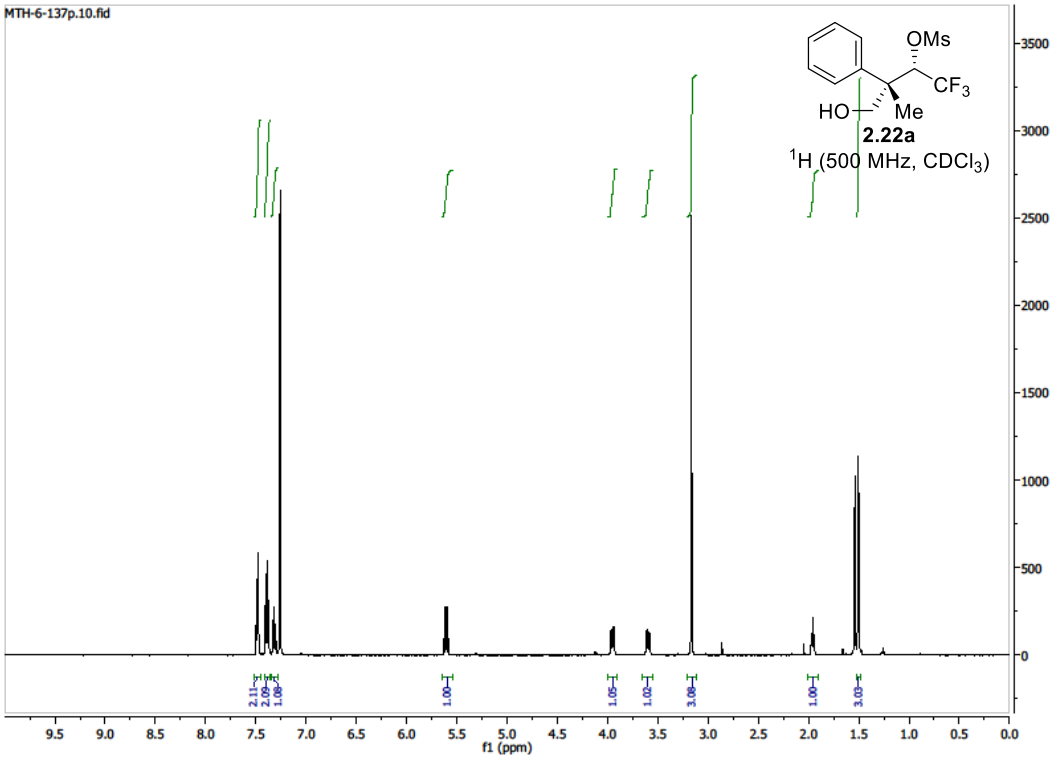
^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.5, 128.7, 127.7, 126.7, 123.5 (q, *J* = 286 Hz), 79.6 (q, *J* = 29 Hz), 68.9, 45.0, 39.2, 15.9.

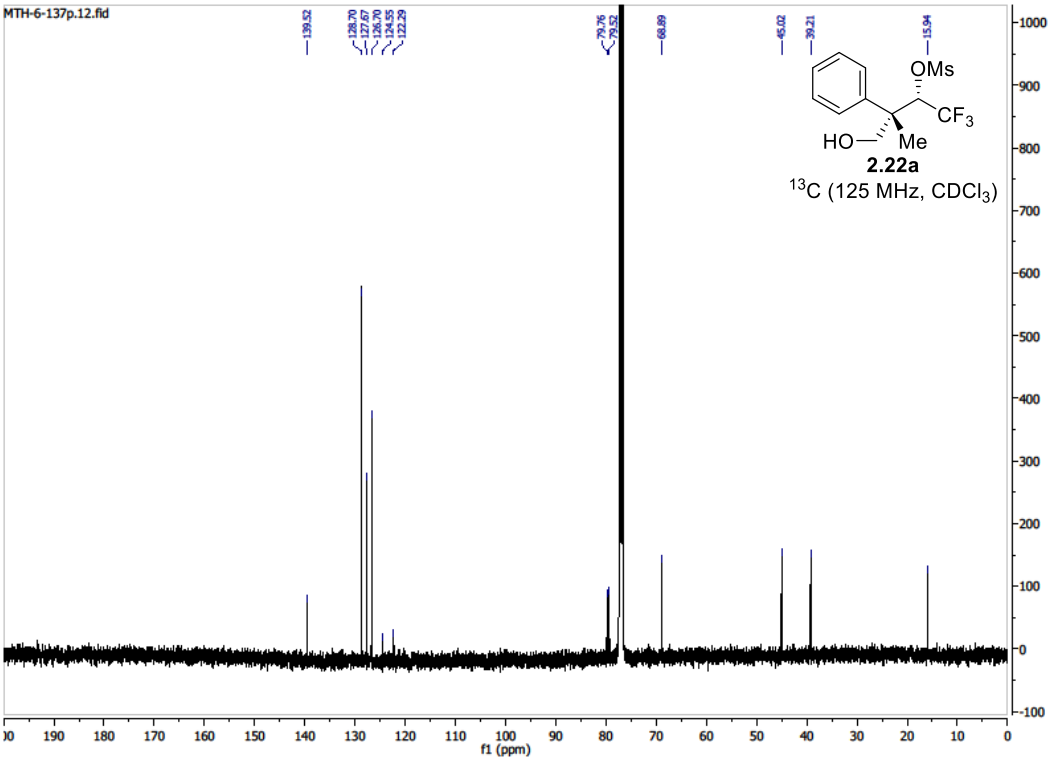
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.1 (d, *J* = 7.4 Hz).

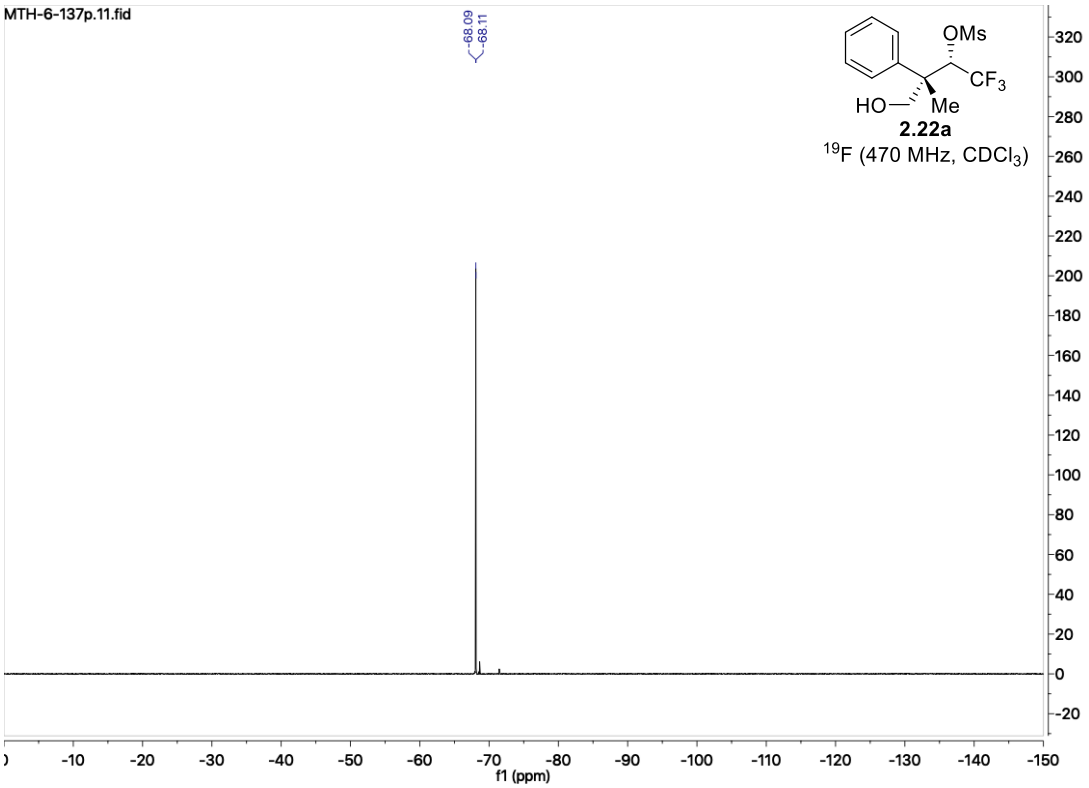
HRMS (ESI+Na, *m/z*) for $C_{12}H_{15}F_3O_4S$: calcd. = 335.0535; found = 335.0532

FTIR (neat): 3539, 2940, 1498, 1357, 1272, 1176, 1051, 1011, 963, 830, 699 cm^{-1}.

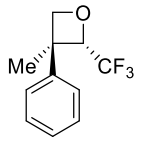
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +21.3 (c = 0.75, $CHCl_3$).


MTH-6-137p.10.fid
OMs
CF3
HO
Me
2.22a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-137p.12.fid
139.52
128.70
127.67
126.70
124.55
122.29
79.76
79.52
68.89
45.02
39.21
15.94
OMs
CF3
HO
Me
2.22a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-137p.11.fid
-68.09
-68.11
OMs
CF3
HO
Me
2.22a
19F (470 MHz, CDCl3)
f1 (ppm)

(2*S*,3*S*)-3-methyl-3-phenyl-2-(trifluoromethyl)oxetane (2.9a)



2.9a

To a stirred solution of mesylate **2.22a** (130 mg, 0.42 mmol) in THF (4.2 mL) in a pressure tube was added NaH (25 mg, 0.63 mmol, 60% w/w in mineral oil). The reaction mixture was heated to 70 °C for 14 hrs. Water (2 mL) was added followed by Et_2O (3 mL) and the phases were separated. The organic phase was washed with water (2 x 2 mL) and the combined aqueous phases were washed with Et_2O (2 x 3 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 94:6 hexanes:ethyl acetate) to afford the title compound **2.9a** (69 mg, 0.32 mmol) as a colorless oil in 76% yield.

R_f = 0.49 (90:10 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.08 (q, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 5.3 Hz, 1H), 4.71 (d, *J* = 5.3 Hz, 1H), 1.67 (q, *J* = 1.5 Hz, 3H).

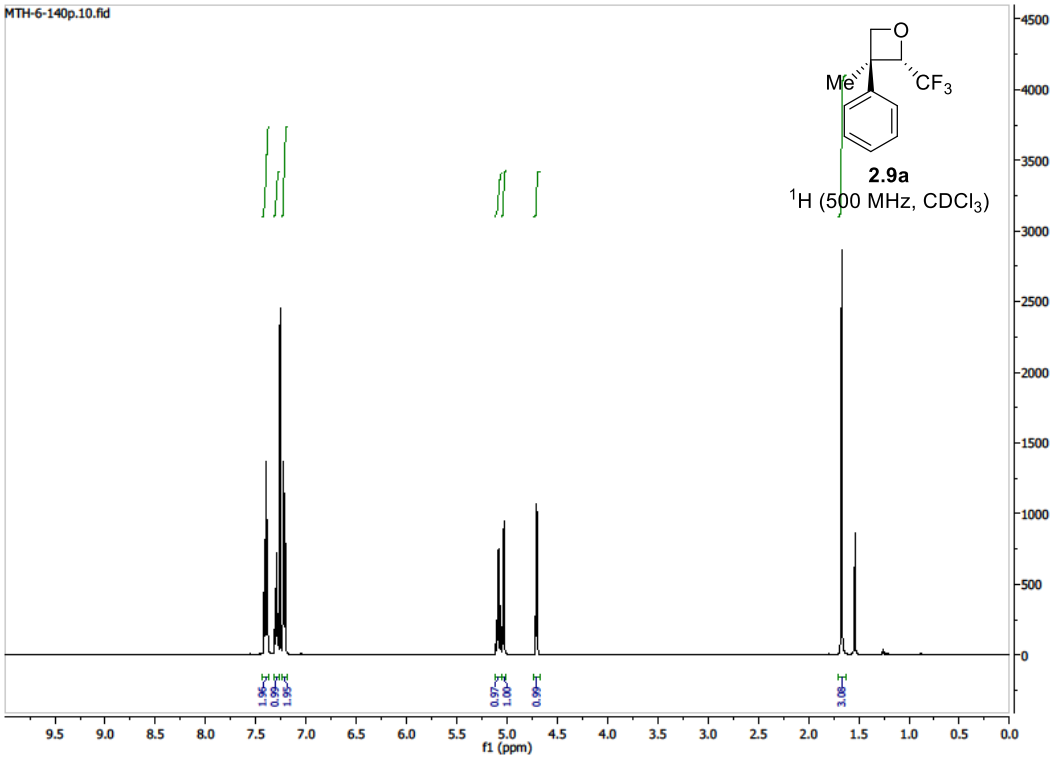
^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.8, 129.0, 127.0, 124.9, 123.9 (q, *J* = 282 Hz), 85.4 (q, *J* = 32 Hz), 82.2, 45.6, 23.7 (q, *J* = 2.3 Hz).

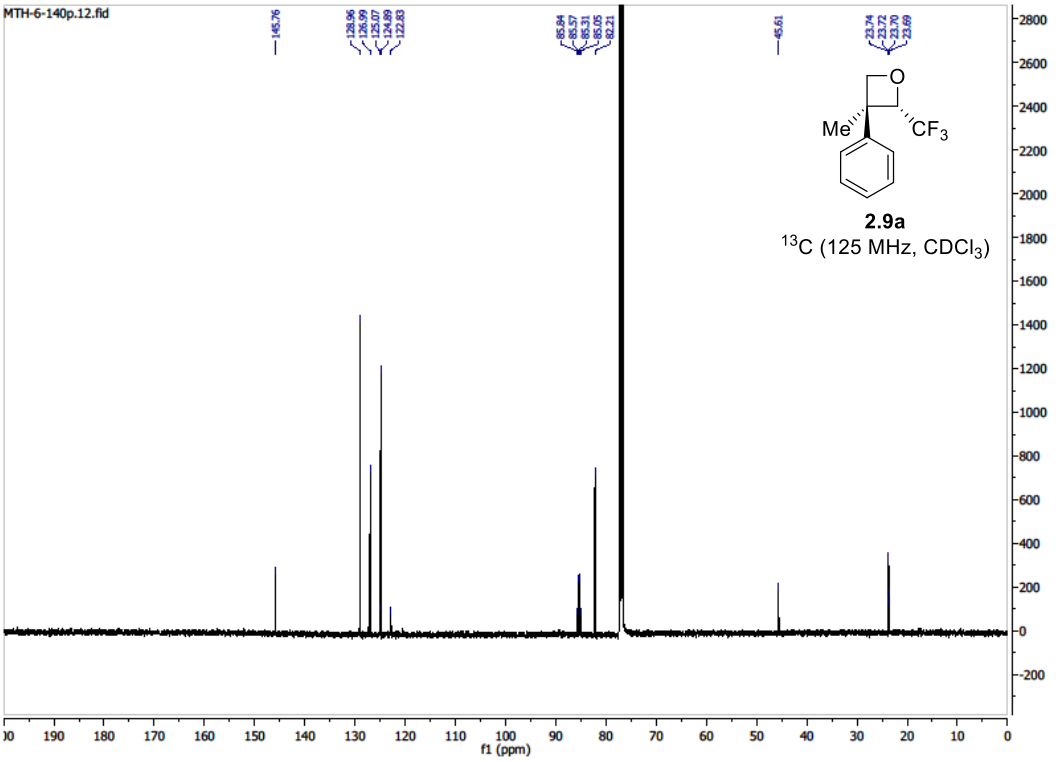
^{19}F NMR (470 MHz, $CDCl_3$) δ: -74.9 (qd, *J* = 1.5, 7.6 Hz).

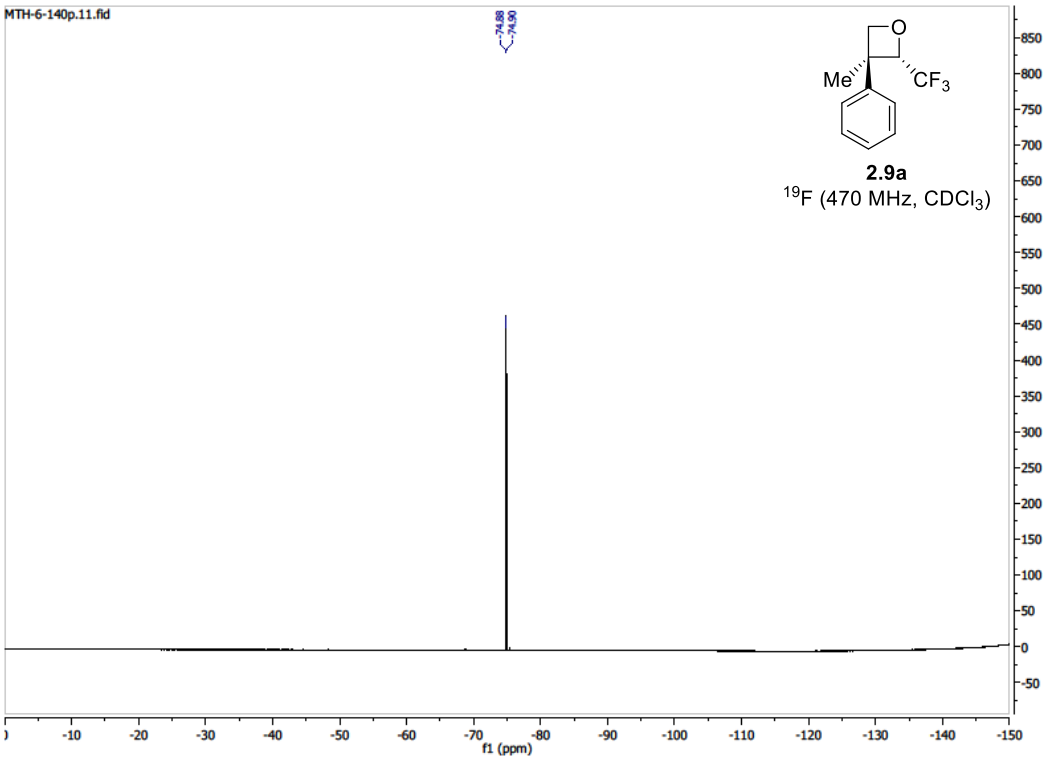
HRMS (CI+, *m/z*) for $C_{11}H_{12}OF_3$: calcd. = 217.0840; found = 217.0842.

FTIR (neat): 2974, 2894, 1498, 1392, 1291, 1153, 1128, 1038, 913, 763, 700 cm^{-1}.

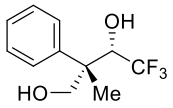
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +32.0 (c = 1.0, $CHCl_3$).


MTH-6-140p.10.fid
Me
CF3
2.9a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-140p.12.fid
Me
CF3
2.9a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-140p.11.fid
-74.88
-74.90
O
Me
CF3
2.9a
19F (470 MHz, CDCl3)
f1 (ppm)

(2*S*,3*S*)-4,4,4-trifluoro-2-methyl-2-phenylbutane-1,3-diol (2.23a)



2.23a

To a stirred flask containing fluoral adduct **2.8a** (94 mg, 0.41 mmol) in CH_2Cl_2 (8 mL) was added MeOH (1 mL) and the reaction mixture cooled to -78 °C. Ozone was bubbled through the solution until the solution turned blue (~5 mins). N_2 was bubbled through the solution to remove the excess ozone. $NaBH_4$ (78 mg, 2.04 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Aqueous 1N HCl (5 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous phase was washed with EtOAc (2 x 5 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 75:25 hexanes:ethyl acetate) to afford the title compound **2.23a** (79 mg, 0.34 mmol) as a colorless oil in 84% yield.

R_f = 0.23 (70:30 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (d, *J* = 7.7 Hz, 2H), 7.38 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 4.61 (q, *J* = 6.5 Hz, 1H), 3.93 (d, *J* = 11.1 Hz, 1H), 3.90 (d, *J* =11.1 Hz, 1H), 3.75 (br d, *J* = 4.0 Hz, 1H, O*H*), 2.22 (br s, 1H, O*H*), 1.47 (q, *J* = 1.4 Hz, 3H).

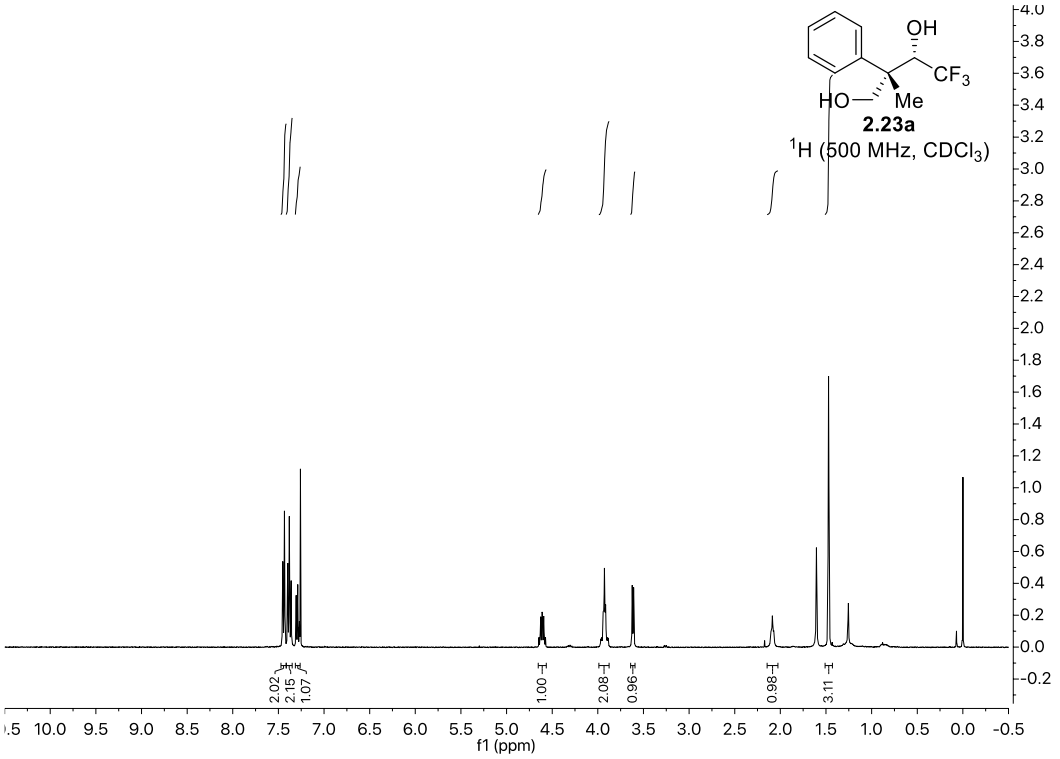
^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.6, 128.7, 127.2, 126.3, 125.2 (q, *J* = 284 Hz), 75.5 (q, *J* = 28 Hz), 70.5, 44.8, 16.8.

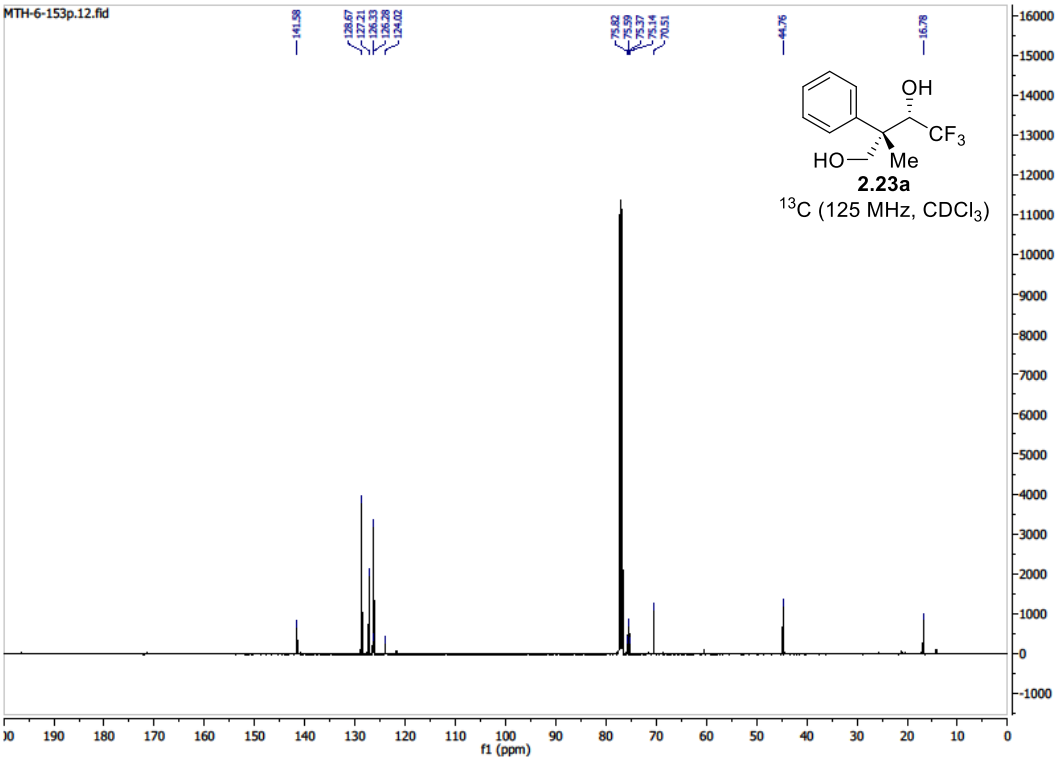
^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.42 (d, *J* = 6.7 Hz).

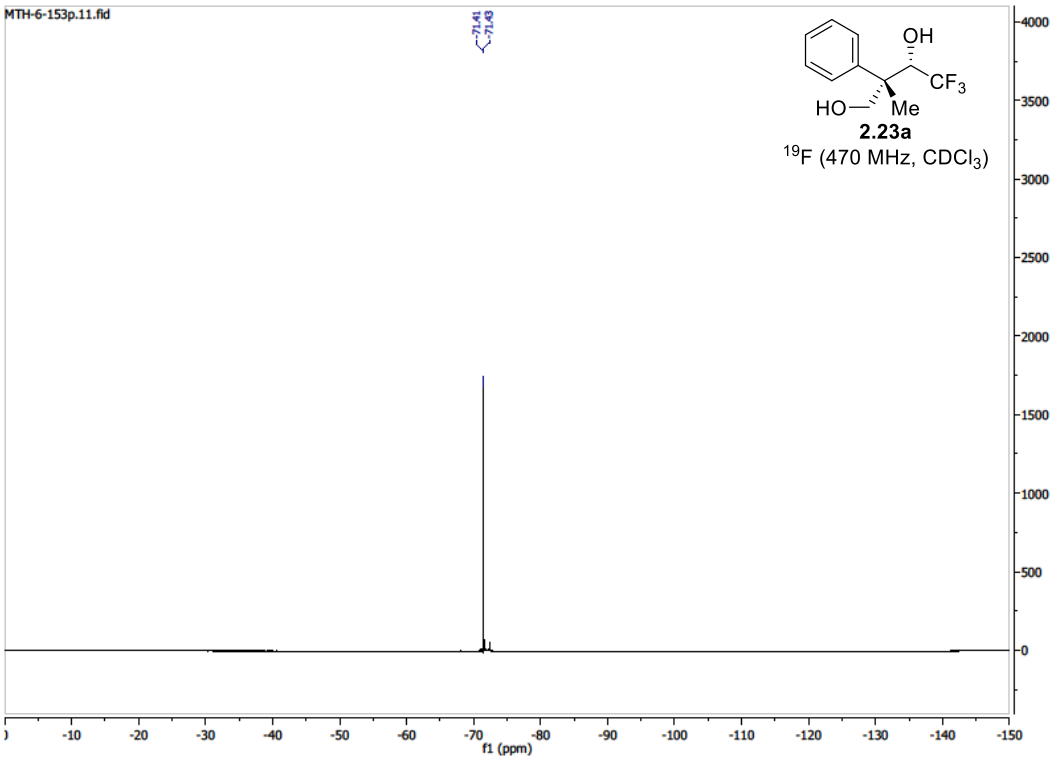
HRMS (EI+, *m/z*) for $C_{11}H_{13}O_2F_3$: calcd. = 234.0868; found = 234.0872.

FTIR (neat): 3365, 29991, 1499, 1266, 1166, 1107, 1027, 700 cm^{-1}.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -4 (c = 1.0, $CHCl_3$).


OH
CF3
HO
Me
2.23a
1H (500 MHz, CDCl3)
2.02
2.15
1.07
1.00
2.08
0.96
0.98
3.11
f1 (ppm)


MTH-6-153p.12.fid
141.58
128.67
127.21
126.33
126.28
124.02
75.62
75.59
75.37
75.14
70.51
44.76
16.78
OH
CF3
HO
Me
2.23a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-153p.11.fid
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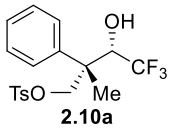
-71.43
OH
CF3
HO
Me
2.23a
19F (470 MHz, CDCl3)
4000
3500
3000
2500
2000
1500
1000
500
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

(2*S*,3*S*)-4,4,4-trifluoro-3-hydroxy-2-methyl-2-phenylbutyl 4-methylbenzenesulfonate (2.10a)



2.10a

To a stirred solution of diol **2.23a** (76 mg, 0.32 mmol) in 2,6-lutidine (0.6 mL, 0.5 M) was added TsCl (124 mg, 0.65 mmol) and the reaction mixture was stirred for 14 hours at room temperature. EtOAc (10 mL) and aqueous 1N HCl (10 mL) were added and the phases separated. The organic phase was washed with aqueous 1N HCl (10 mL). The combined aqueous phases were washed with EtOAc (2 x 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 80:20 hexanes:EtOAc) to afford the title compound **2.10a** (93 mg, 0.24 mmol) as a white solid in 75% yield.

R_f = 0.34 (70:30 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.5 Hz, 2H), 7.30-7.22 (m, 7H), 4.52 (dq, *J* = 6.9 Hz, 6.9 Hz, 1H), 4.41 (d, *J* = 9.5 Hz, 1H), 3.88 (d, *J* = 9.5 Hz, 1H), 2.91 (d, *J* = 6.9 Hz, 1H, O*H*), 2.41 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.1, 139.6, 132.2, 129.9, 128.4, 127.9, 127.4, 126.6, 124.9 (q, *J* = 285 Hz), 74.6 (q, *J* = 1 Hz), 72.6 (q, *J* = 29 Hz), 44.2, 21.7, 16.0 (q, *J* = 2 Hz).

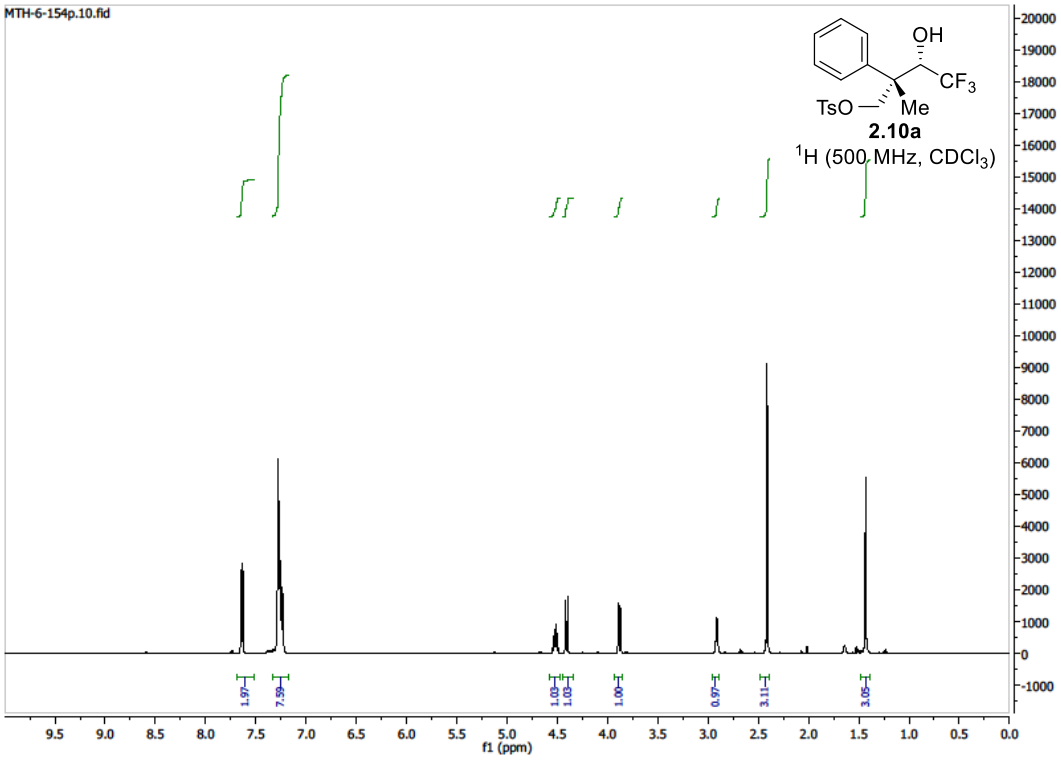
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.6 (d, *J* = 6.9 Hz).

HRMS (ESI+Na, *m/z*) for $C_{18}H_{19}F_3N_4S$: calcd. = 411.0848; found = 411.0848

FTIR (neat): 3504, 3044, 1599, 1355, 1172, 977, 812 cm^{-1}.

$[\alpha]_D^{24}$**=** -4 (c = 1.0, $CHCl_3$).

MP =84-87 °C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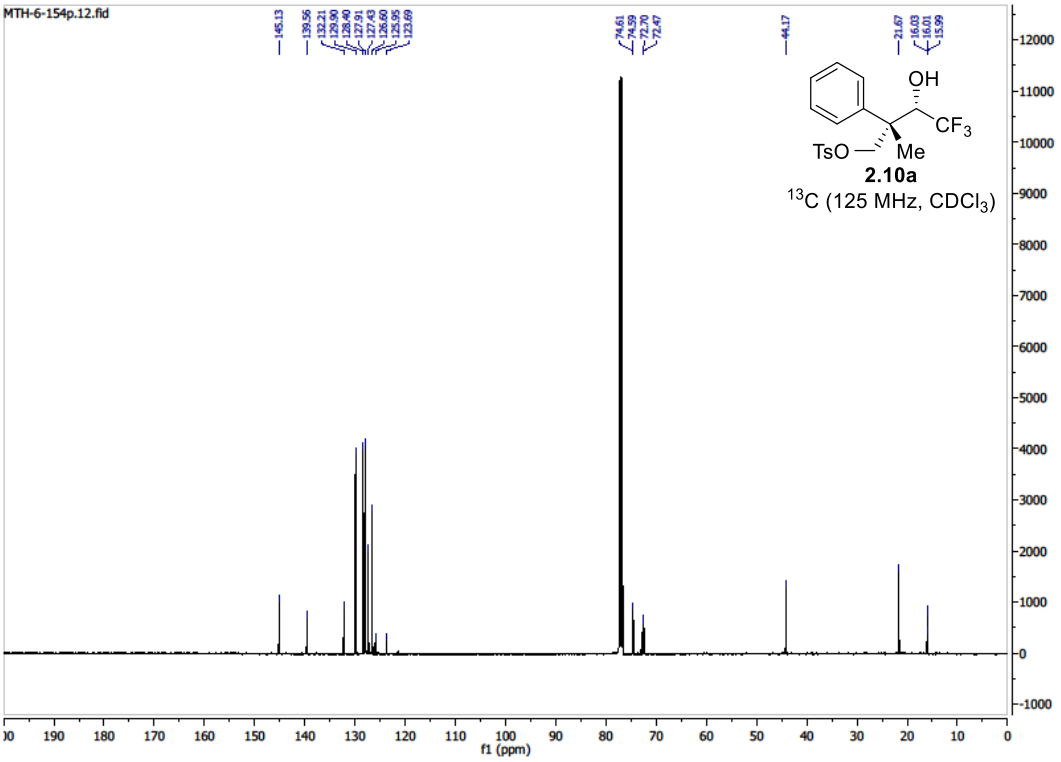
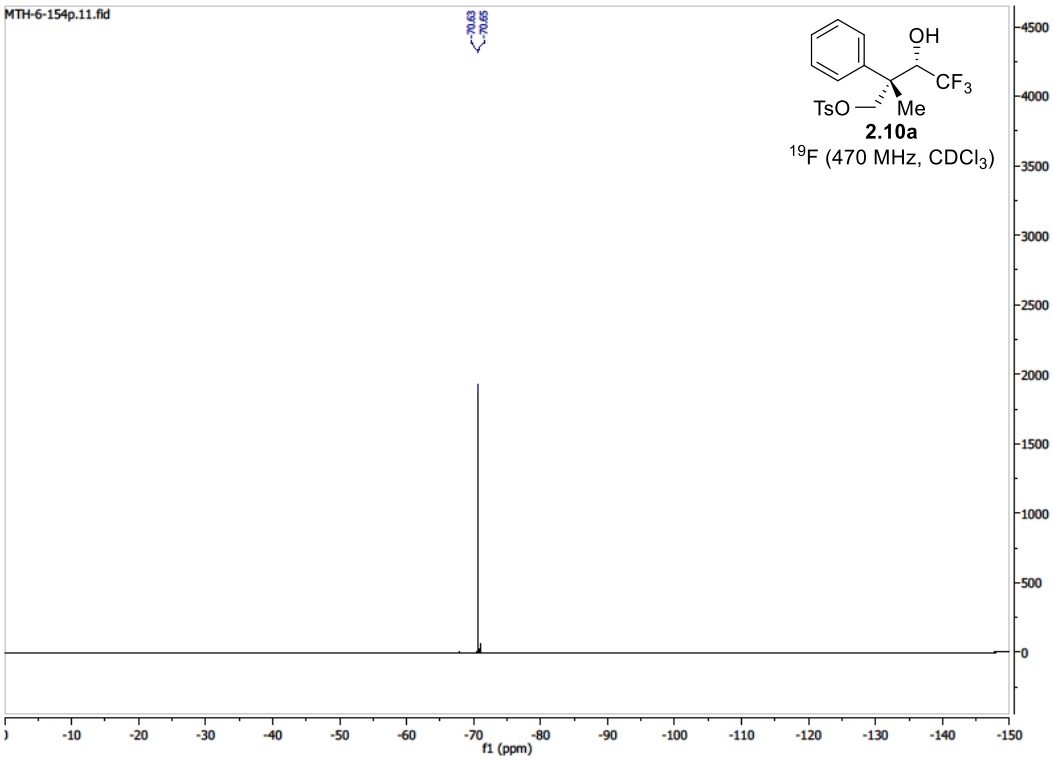
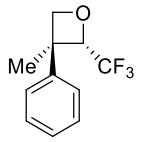
OH
CF3
TsO
Me
2.10a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-154p.12.fid
OH
CF3
TsO
Me
2.10a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-154p.11.fid
-70.63
-70.65
OH
CF3
TsO
Me
2.10a
19F (470 MHz, CDCl3)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

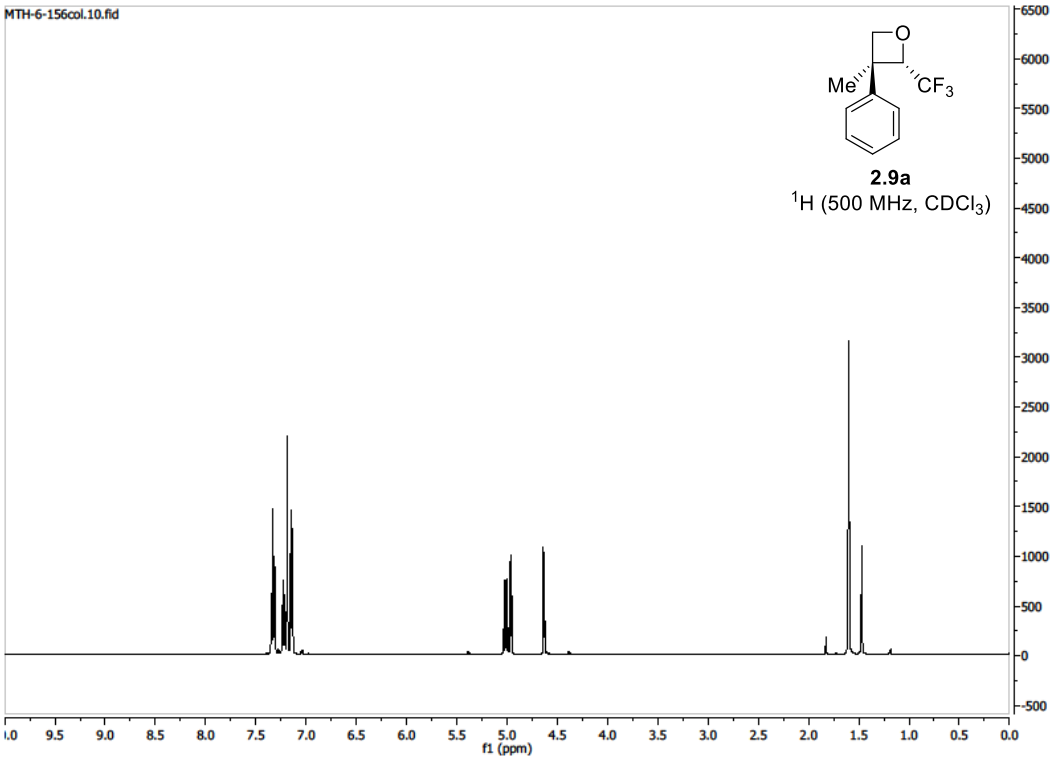
(2*S*,3*S*)-3-methyl-3-phenyl-2-(trifluoromethyl)oxetane (2.9a)



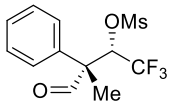
2.9a

To a stirred solution of tosyl protected alcohol **2.10a** (71 mg, 0.18 mmol) in THF (1 mL) in a pressure tube was added NaH (11 mg, 0.27 mmol, 60% w/w in mineral oil). The reaction mixture was heated to 25 °C for 14 hrs. Water (2 mL) was added followed by Et_2O (3 mL) and the phases were separated. The organic phase was washed with water (2 x 2 mL) and the combined aqueous phases were washed with Et_2O (2 x 3 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 93:7 hexanes:ethyl acetate) to afford the title compound **2.9a** (27 mg, 0.12 mmol) as a colorless oil in 68% yield.

The data collected on this sample was in total agreement with the data collected above through the reaction of mesyl protected alcohol **2.22a**.


MTH-6-156col.10.fid
O
Me
CF3
2.9a
1H (500 MHz, CDCl3)
f1 (ppm)

(2S,3R)-1,1,1-trifluoro-3-methyl-4-oxo-3-phenylbutan-2-yl methanesulfonate (2.24a)



2.24a

A stirred flask containing mesylate **2.21a** (154 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 °C. Ozone was bubbled through the solution until the solution turned blue (~5 mins). N_2 was bubbled through the solution to remove the excess ozone. PPh_3 (197 mg, 0.75 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 85:15 hexanes:EtOAc) to afford the title compound **2.24a** (142 mg, 0.46 mmol) as a light yellow solid in 92% yield.

R_f = 0.18 (85:15 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.34 (s, 1H), 7.44 (dd, *J* = 8.1, 8.1 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.76 (q, *J* = 6.5 Hz, 1H), 3.11 (s, 3H), 1.77 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.4, 132.4, 129.5, 129.2, 128.0, 123.2 (q, *J* = 282 Hz), 77.8 (q, *J* = 29.9 Hz), 55.4, 39.6, 13.9.

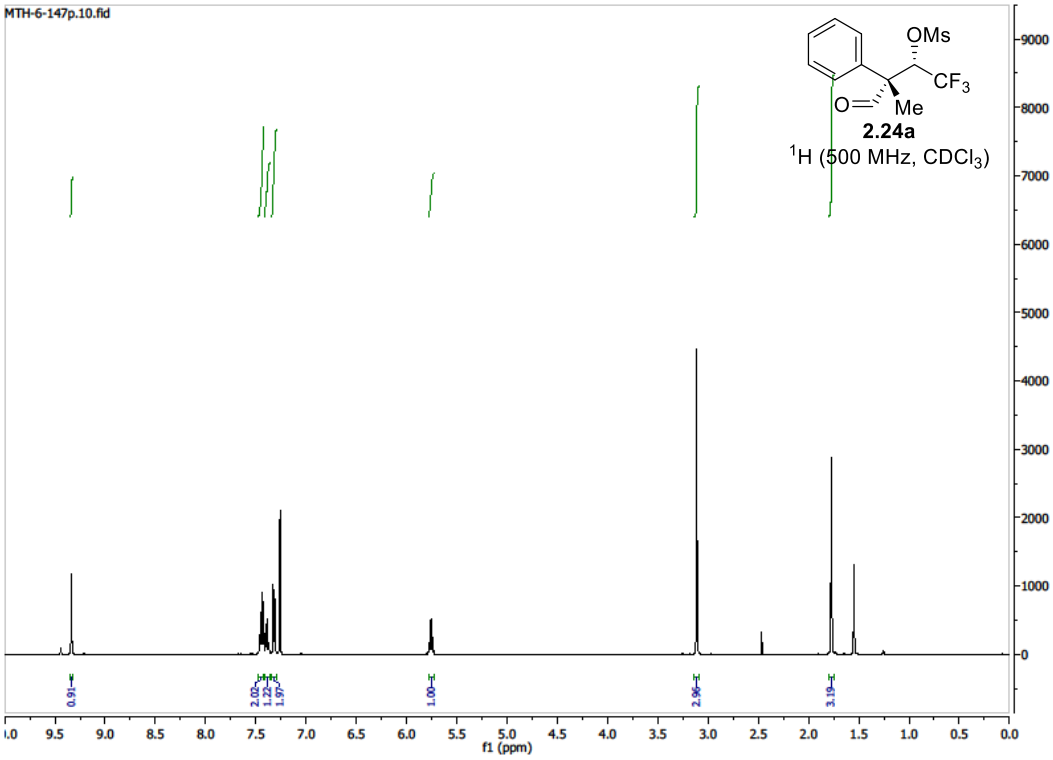
^{19}F NMR (470 MHz, $CDCl_3$) δ: -68.7 (d, *J* = 6.5 Hz).

HRMS (ESI+Na, *m/z*) for $C_{12}H_{13}F_3O_4S$: calcd. = 333.0379; found = 333.0378

FTIR (neat): 3041, 1727, 1497, 1360, 1270, 1179, 1021, 966, 830 cm^{-1}.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +46 (c = 0.3, $CHCl_3$).

MP = 94-97 °C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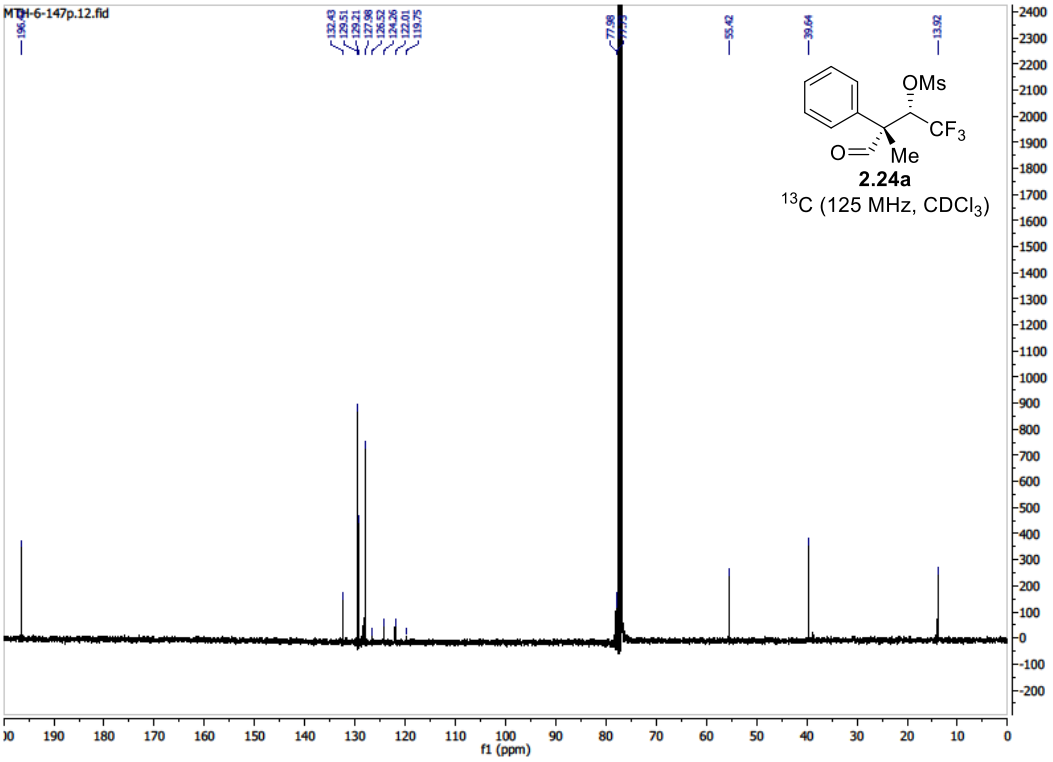
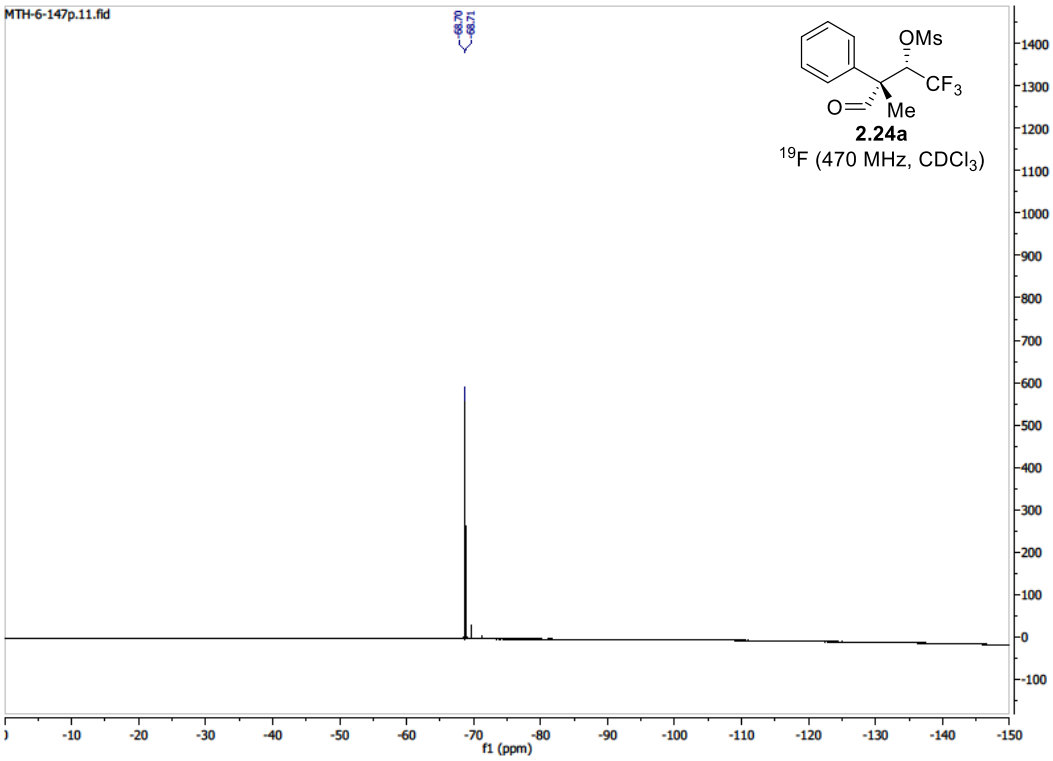
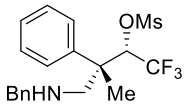
OMs
CF3
O
Me
2.24a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-147p.12.fid
OMs
CF3
O
Me
2.24a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-147p.11.fid
-68.70
-68.71
OMs
CF3
O
Me
2.24a
19F (470 MHz, CDCl3)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

(2*S*,3*S*)-4-(benzylamino)-1,1,1-trifluoro-3-methyl-3-phenylbutan-2-yl methanesulfonate (2.25a)



2.25a

To a stirred solution of aldehyde **2.24a** (83 mg, 0.26 mmol) in toluene (0.8 mL) was added AcOH (0.015 mL, 0.26 mmol) followed by benzyl amine (0.057 mL, 0.52 mmol) and 4 Å molecular sieves (80 mg). The reaction mixture was heated to 60 °C for 1 hour. The reaction mixture was cooled to 0 °C and $NaBH_3CN$ (25 mg, 0.42 mmol) was added in a single portion. The reaction mixture was stirred at 25 °C for 3 hours. Saturated aqueous $NaHCO_3$ (2 mL) was added followed by EtOAc (3 mL) and the phases were separated. The organic phase was washed with water (2 x 2mL) and the combined aqueous phases were washed with EtOAc (2 x 2 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 88:12 hexanes:EtOAc) to afford the title compound **2.25a** (79 mg, 0.20 mmol) as a light yellow oil in 76% yield.

R_f = 0.26 (85:15 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.27 (m, 3H, 7.22 (m, 3H), 5.59 (q, *J* = 6.5 Hz, 1H), 3.72 (d, *J* = 12.2 Hz, 1H), 3.66 (d, *J* = 12.2 Hz, 1H), 3.11 (d, *J* = 12.2 Hz, 1H), 3.09 (s, 3H), 2.78 (d, *J* = 12.2 Hz, 1H), 1.58 (s, 3H).

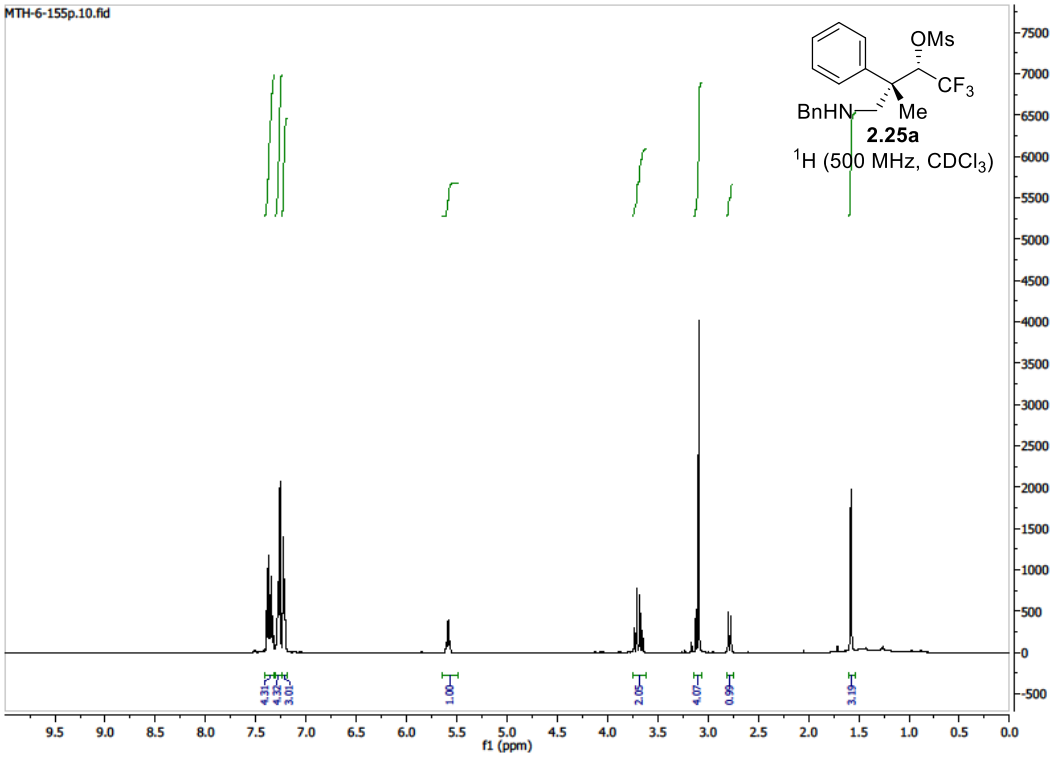
^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.2, 140.1, 128.6, 128.3, 128.1, 127.3, 126.9, 126.7, 123.5 (q, *J* = 284 Hz), 81.3 (q, *J* = 29 Hz), 57.0, 54.1, 44.3, 39.3, 17.7.

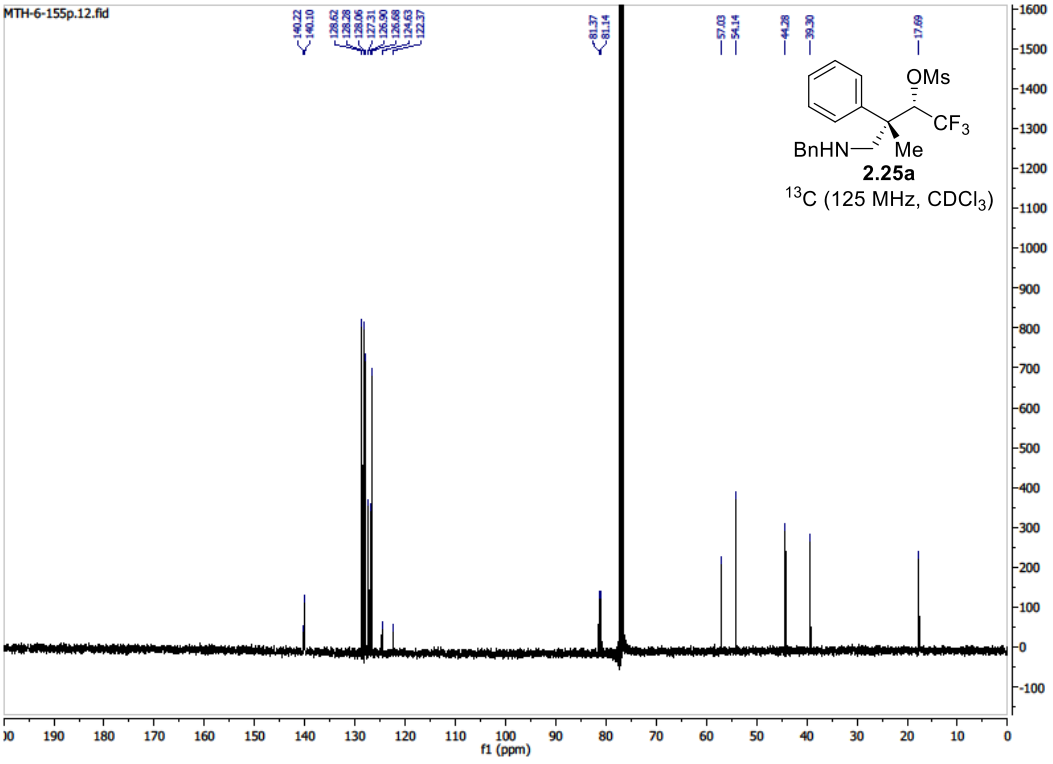
^{19}F NMR (470 MHz, $CDCl_3$) δ: -67.8 (d, *J* = 6.5 Hz).

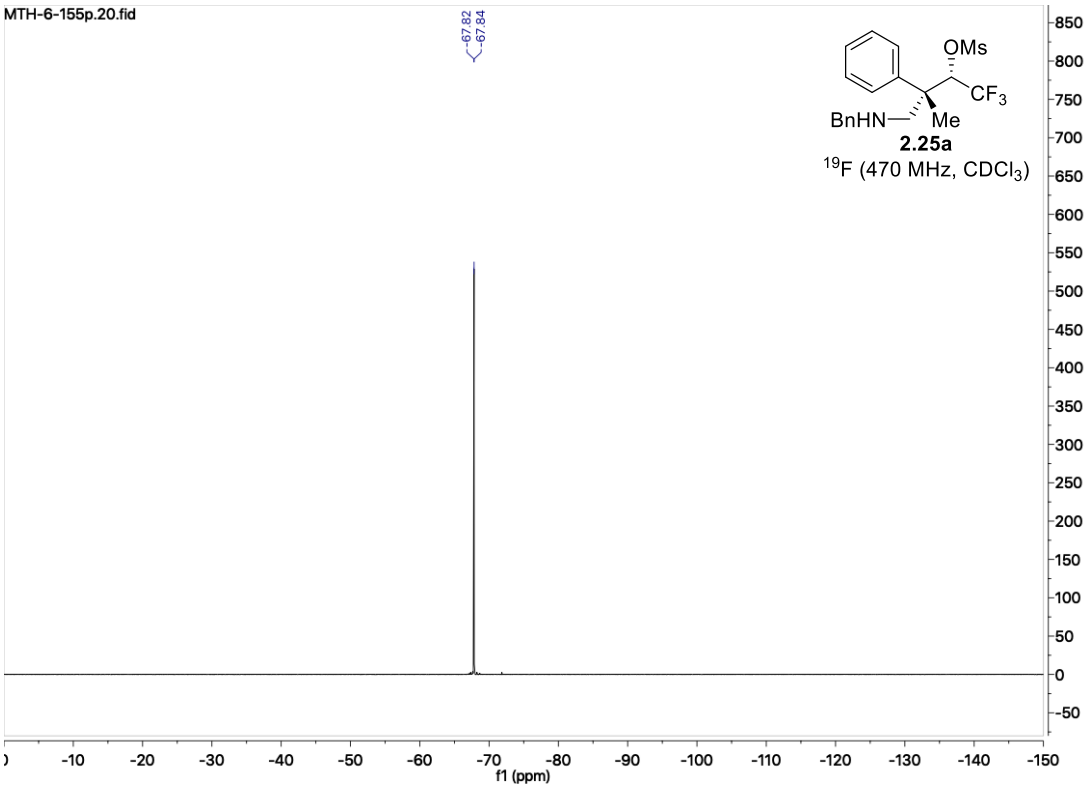
HRMS (ESI+H, *m/z*) for $C_{19}H_{22}F_3NO_3S$: calcd. = 402.1345; found = 402.1343

FTIR (neat): 3736, 3030, 2924, 1449, 1361, 1179, 963, 832, 699 cm^{-1}.

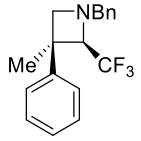
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= +4 (c = 1.0, $CHCl_3$).


MTH-6-155p.10.fid
OMs
CF3
BnHN
Me
2.25a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-155p.12.fid
140.22
140.10
126.62
128.28
128.06
127.31
126.90
126.68
124.63
122.37
81.37
81.14
57.03
54.14
44.28
39.30
17.69
OMs
CF3
BnHN
Me
2.25a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-155p.20.fid
-67.82
-67.84
OMs
CF3
BnHN
Me
2.25a
19F (470 MHz, CDCl3)
f1 (ppm)

(2*R*,3*S*)-1-benzyl-3-methyl-3-phenyl-2-(trifluoromethyl)azetidine (2.11a)



2.11a

To a stirred solution of amine **2.25a** (40 mg, 0.1 mmol) in *m*-xylenes (0.5 mL) in a sealable tube was added K_2CO_3 (28 mg, 0.2 mmol). The reaction mixture was heated to 140 °C for 20 hours in a microwave reactor. The reaction mixture was cooled to 25 °C, filtered and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 95:5 hexanes:EtOAc) to afford the title compound **2.11a** (13.5 mg, 0.045 mmol) as a colorless oil in 45% yield along with recovered starting material (12.8 mg, 0.032 mmol).

R_f = 0.48 (90:10 hexanes:EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 7.2 Hz, 2H), 7.39-7.25 (m, 8H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.90 (d, *J* = 7.0 Hz, 1H), 3.68 (q, *J* = 7.3 Hz, 1H), 3.61 (d, *J* = 14.0 Hz, 1H), 2.98 (d, *J* = 7.0 Hz, 1H), 1.63 (s, 3H).

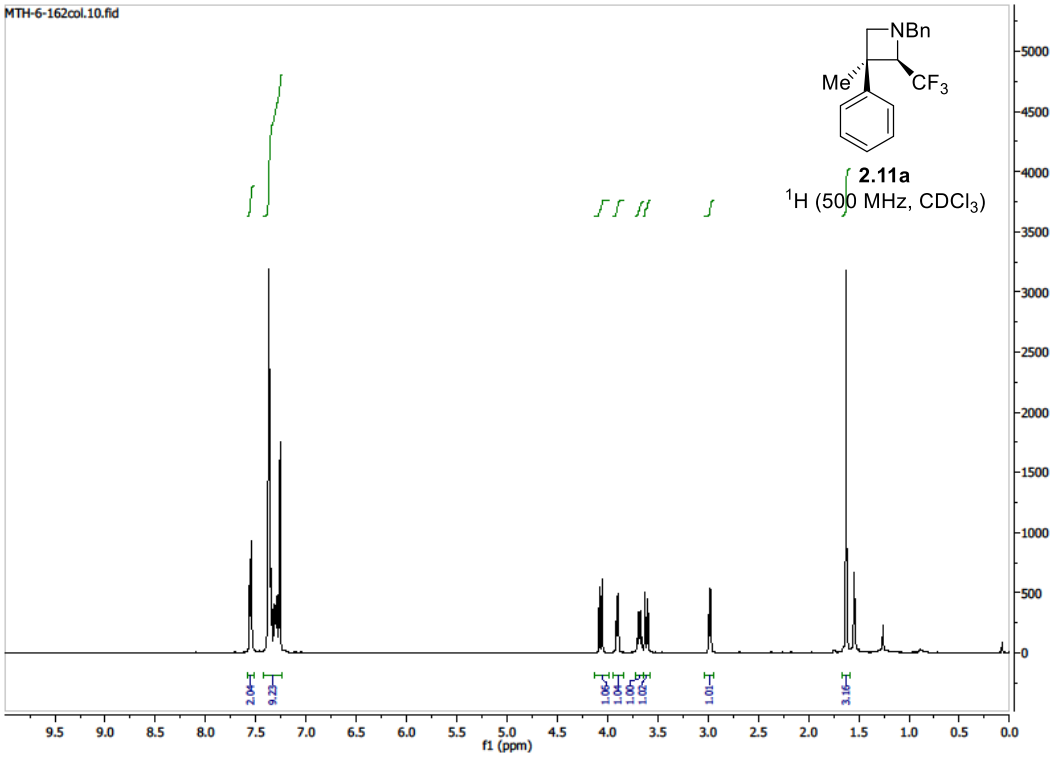
^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.6, 136.8, 128.8, 128.4, 127.9, 127.4, 127.3, 126.9, 124.4 (q, *J* = 280 Hz), 73.2 (q, *J* = 29 Hz), 63.3, 61.3, 40.8, 28.1.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.6 (d, *J* = 7.3 Hz).

HRMS (ESI+H, *m/z*) for $C_{18}H_{18}F_3N$: calcd. = 306.1464; found = 306.1465

FTIR (neat): 3029, 2927, 2851, 1497, 1294, 1127, 1030, 697 cm^{-1}.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= -8.8 (c = 0.2, $CHCl_3$).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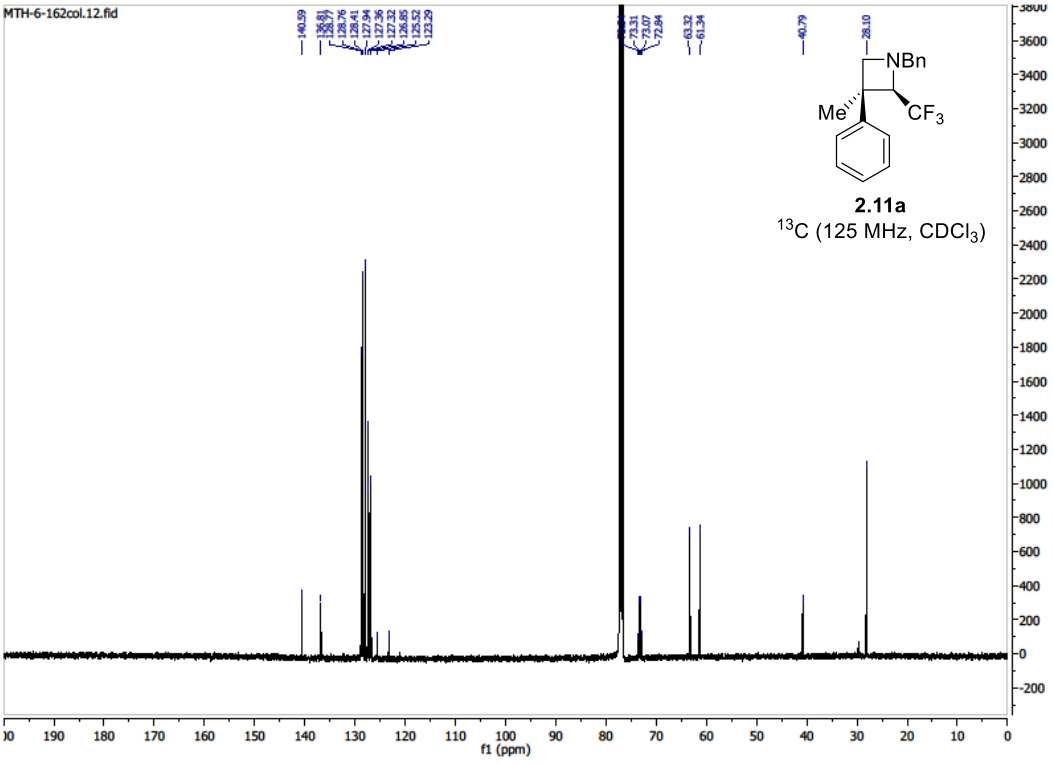
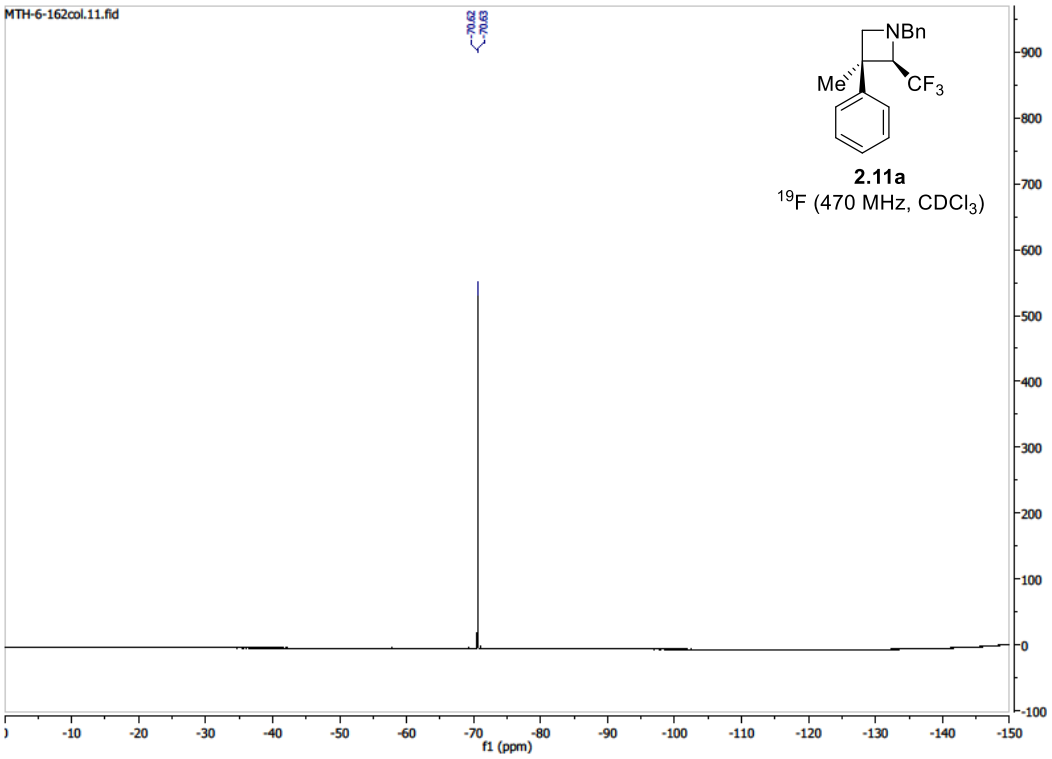
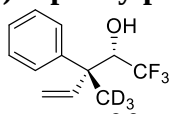
Me
CF3
2.11a
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-162col.12.fid
NBn
Me
CF3
2.11a
13C (125 MHz, CDCl3)
f1 (ppm)


MTH-6-162col.11.fid
-70.62
-70.63
NBn
Me
CF3
2.11a
19F (470 MHz, CDCl3)
900
800
700
600
500
400
300
200
100
0
-100
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

2.5.4.5 Isotopic Labeling Studies

(2*S*,3*R*)-1,1,1-trifluoro-3-(methyl-d3)-3-phenylpent-4-en-2-ol (d*euterio*-2.8a*)*



deuterio-**2.8a**

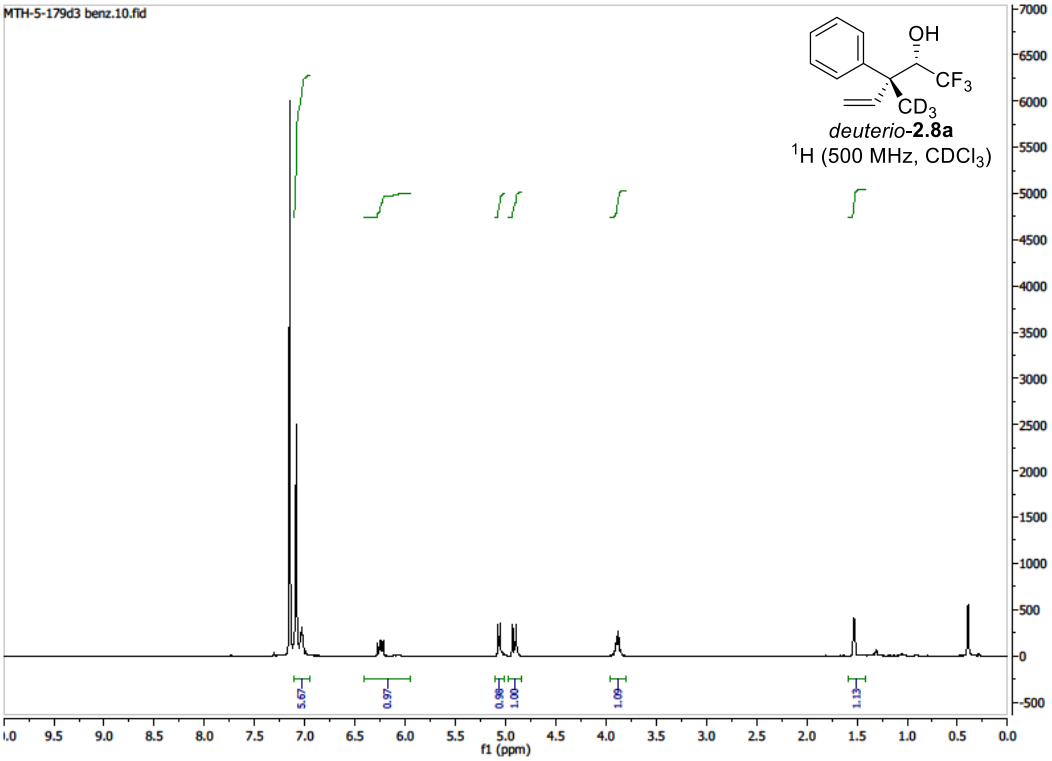
1,1-Disubstituted allene *Deuterio*-1a (52 mg, 0.4 mmol) was subjected to general procedure K. Upon flash column chromatography (SiO_2, 4:96 EtOAc:hexanes), the title compounds 3a (33.2 mg, 0.14 mmol, 17:1 dr) was obtained as a yellow oil in 71% yield.

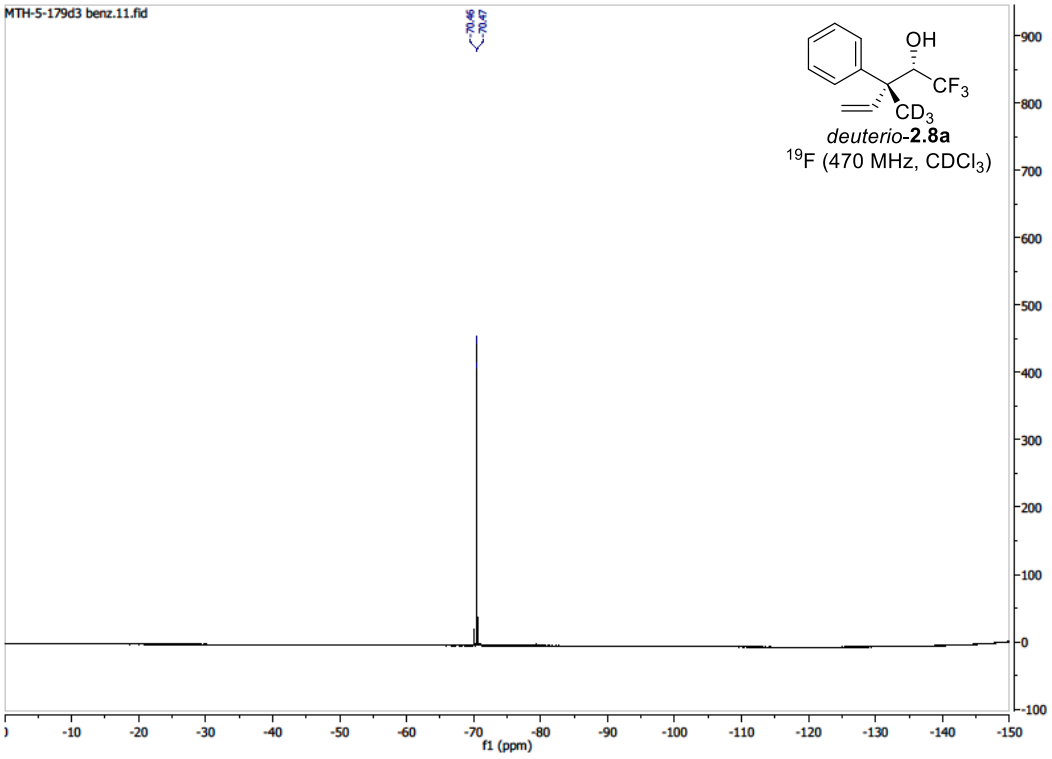
R_f = 0.41 (90:10 hexanes : EtOAc)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.12-6.98 (m, 5H), 6.25 (dd, *J* = 10.5, 14.5 Hz, 1H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 14.5 Hz, 1H), 3.88 (dq, *J* = 7 Hz, 1H), 1.53 (d, *J* = 7 Hz, 1H, O*H*).

^{19}F NMR (470 MHz, C_6D_6) δ: -70.5 (d, *J* = 7 Hz)

HRMS (CI, *m/z*) for $C_{12}H_9D_3OF_3$: calcd. = 232.1029; found = 232.1018


MTH-5-179d3 benz.10.fid
OH
CF3
CD3
deuterio-2.8a
1H (500 MHz, CDCl3)
5.67
0.97
0.98
1.00
1.09
1.13
f1 (ppm)


MTH-5-179d3 benz.11.fid
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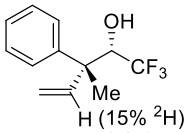
-70.47
OH
CF3
CD3
deuterio-2.8a
19F (470 MHz, CDCl3)
f1 (ppm)

(2S,3R)-1,1,1-trifluoro-3-methyl-3-phenylpent-4-en-4-d-2-ol (*deuterio*-2.8a')



deuterio-**2.8a'**

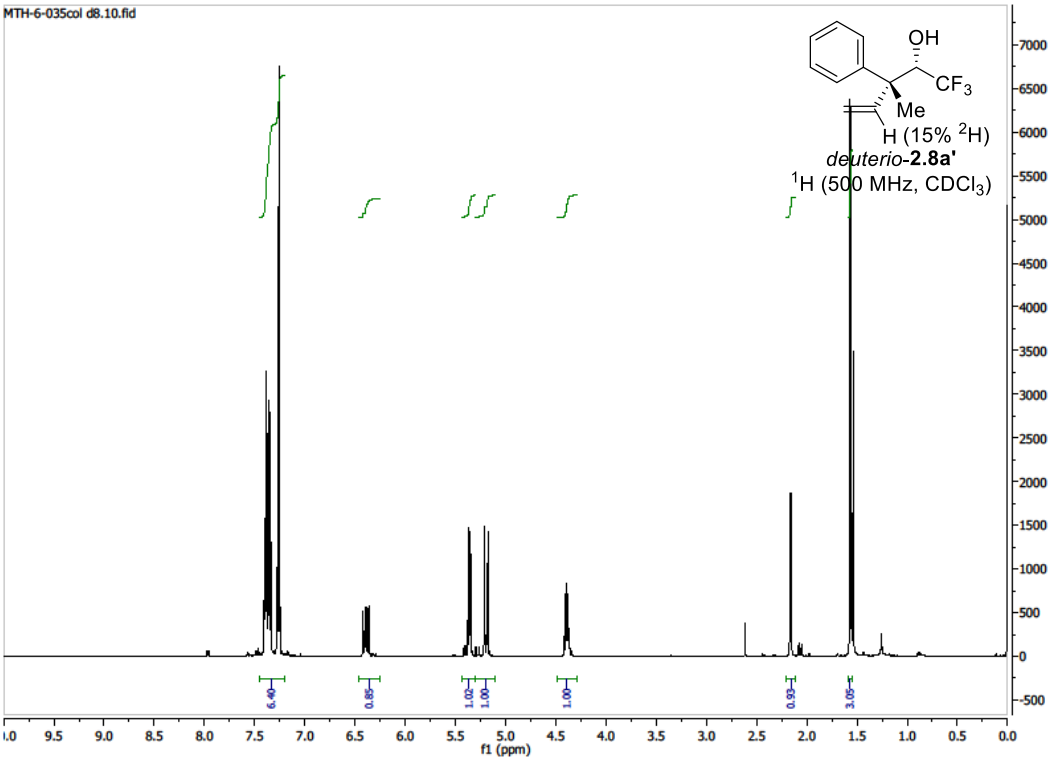
1,1-Disubstituted allene **2.6a** (52 mg, 0.4 mmol) was subjected to general procedure K using d_8-2-PrOH. Upon flash column chromatography (SiO_2, 4:96 EtOAc:hexanes), the title compound **2.8a'** (35.0 mg, 0.16 mmol, 17:1 dr) was obtained as a yellow oil in 75% yield.

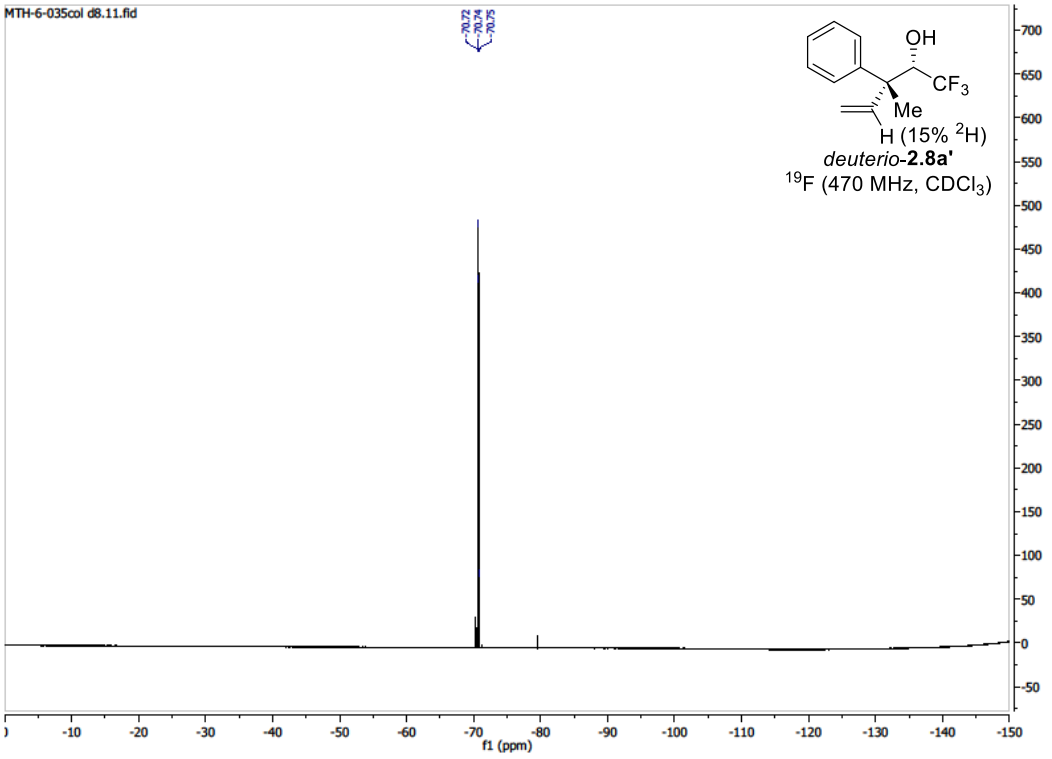
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.34 (m, 4H), 7.26 (m, 1H), 6.39 (dd, *J* = 11.1, 17.8 Hz, 1H), 5.36 (d, *J* = 11.1 Hz, 1H), 5.20 (d, *J* = 17.8 Hz, 1H), 4.39 (dq, *J* = 6.0, 7.9 Hz, 1H), 2.19 (d, *J* = 6.0 Hz, 1H, O*H*), 1.57 (s, 3H).

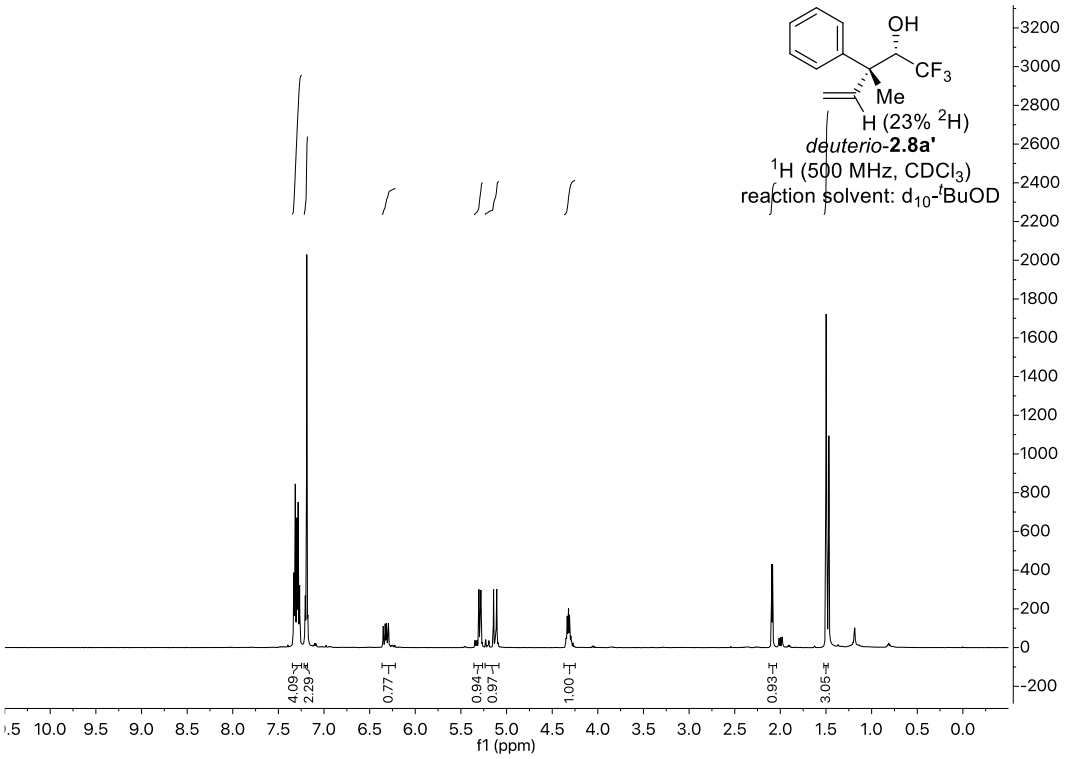
^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.73 (d, *J* = 7.9 Hz, non-deuterated), -70.75 (d, *J* = 7.9 Hz, deuterated).

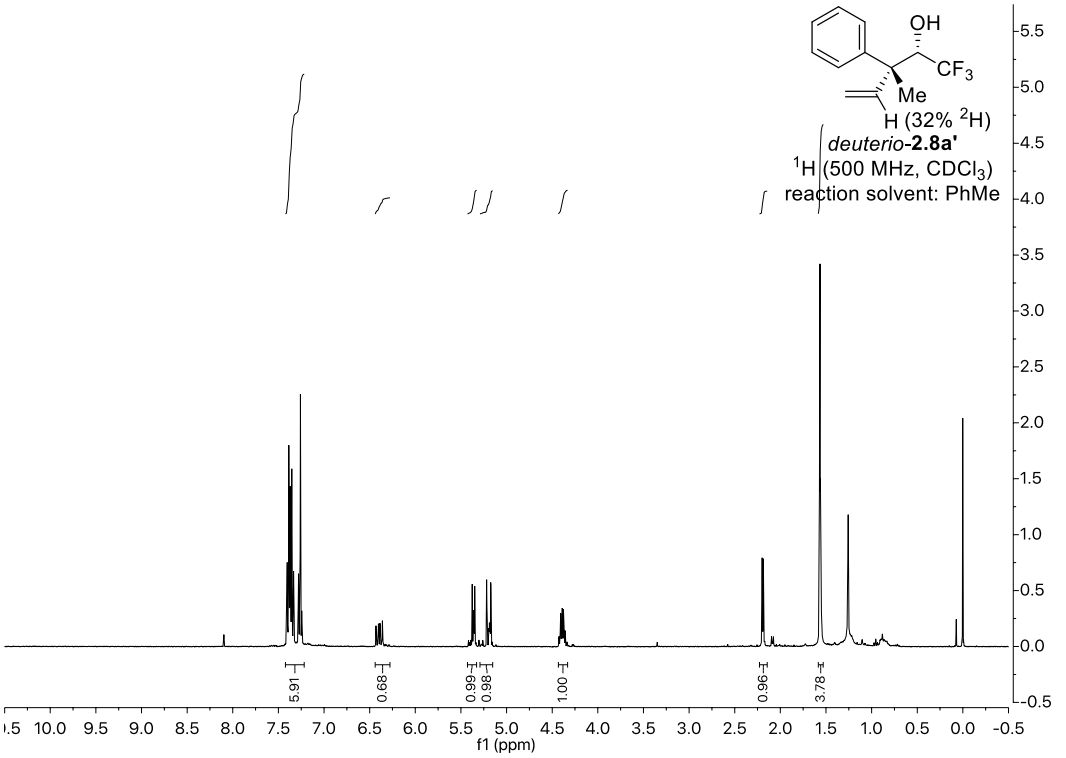
HRMS (CI, *m/z*) for $C_{12}H_{11}DOF_3$: calcd. = 230.0903; found = 230.0933.

Reaction was also conducted in d_{10}-*tert*-butanol and toluene in attempts to increase deuterium incorporation.


MTH-6-035col d8.10.fid
OH
CF3
Me
H (15% 2H)
deuterio-2.8a'
1H (500 MHz, CDCl3)
f1 (ppm)


MTH-6-035col d8.11.fid
-70.72
-70.74
-70.75
OH
CF3
Me
H (15% 2H)
deuterio-2.8a'
19F (470 MHz, CDCl3)
f1 (ppm)


OH
CF3
Me
H (23% 2H)
deuterio-2.8a'
1H (500 MHz, CDCl3)
reaction solvent: d10-tBuOD
4.09
2.29
0.77
0.94
0.97
1.00
0.93
3.05
f1 (ppm)

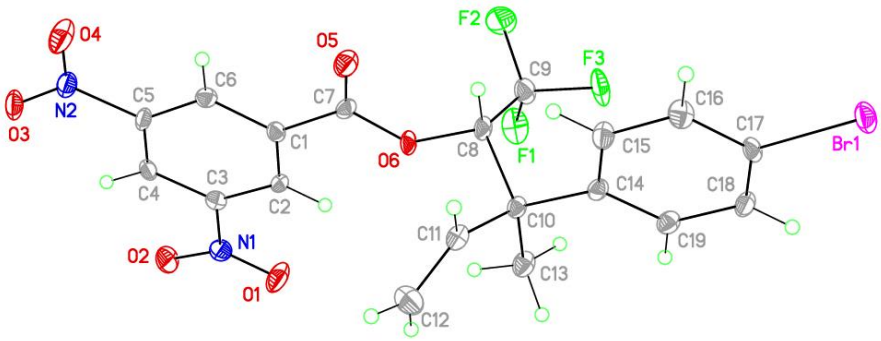

OH
CF3
Me
H (32% 2H)
deuterio-2.8a'
1H (500 MHz, CDCl3)
reaction solvent: PhMe
5.91
0.68
0.99
0.98
1.00
0.96
3.78
f1 (ppm)

2.5.4.6 Crystallographic Material for Coupling Product 2.8d (3,5-Dinitrobenzoate Derivative)

Single Crystal Diffraction Data for Coupling Product 2.8d

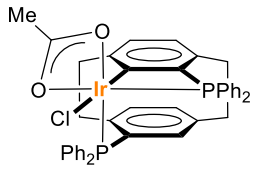
Empirical formula	C19 H14 Br F3 N2 O6	
Formula weight	503.23	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.4648(11) Å	□= 90°.
	b = 7.4731(7) Å	□= 94.863(4)°.
	c = 11.5835(11) Å	□= 90°.
Volume	988.87(16) $Å^3$	
Z	2	
Density (calculated)	1.690 Mg/m^3	
Absorption coefficient	2.147 mm^{-1}	
F(000)	504	
Crystal size	0.34 x 0.22 x 0.18 mm^3	
Theta range for data collection	2.400 to 30.525°.	
Index ranges	-16<=h<=16, -10<=k<=10, -16<=l<=16	
Reflections collected	30981	
Independent reflections	5960 [R(int) = 0.0407]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Numerical	
Max. and min. transmission	0.7386 and 0.6021	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5960 / 1 / 281	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0524	
R indices (all data)	R1 = 0.0324, wR2 = 0.0537	
Absolute structure parameter	0.034(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.340 and -0.382 $e.Å^{-3}$	

Figure 2.9 Crystal Structure of **2.8d** 3,5-Dinitrobenzoate Derivative



View of **2.8d 3,5-**dinitrobenzoate derivative showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

2.5.4.7 Procedure and Spectral Data for Ir-PP-I



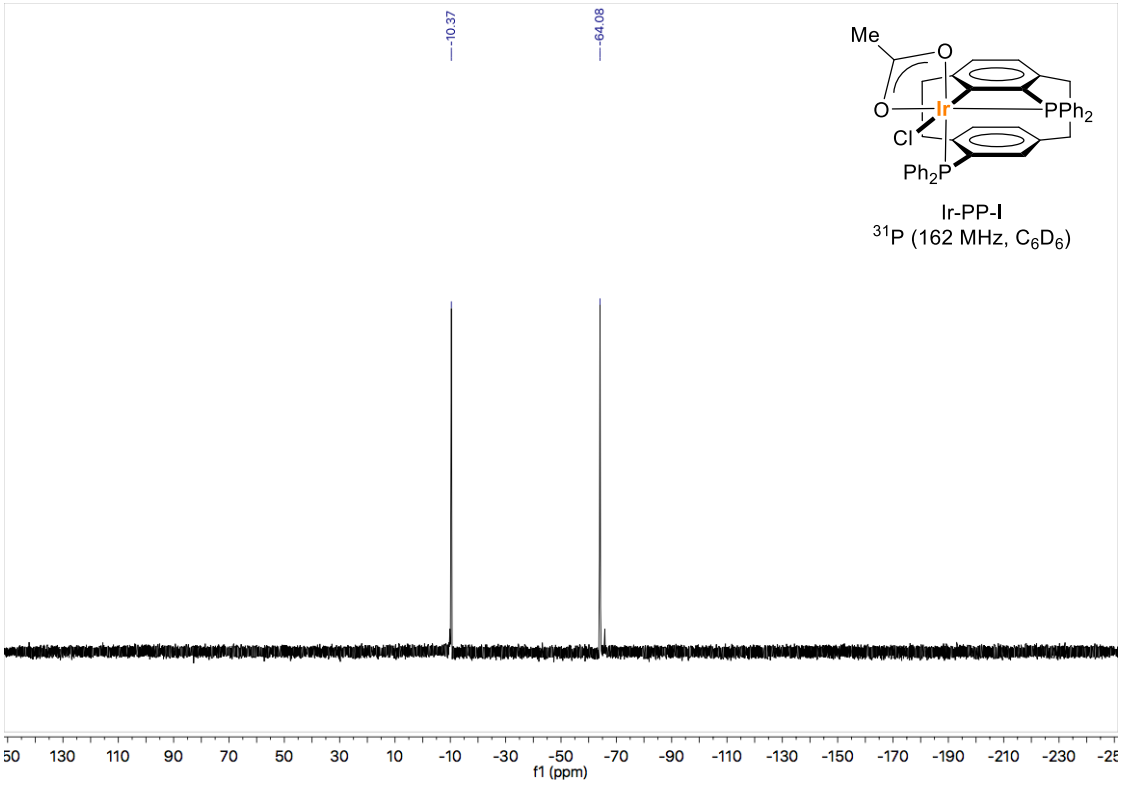
Ir-PP-**I**

A sealed tube equipped with a magnetic stir bar was charged with $[Ir(cod)Cl]_2$ (10 mg, 0.015 mmol, 100 mol %) and (*R*)-PhanePhos (17.3 mg, 0.03 mmol, 200 mol %). The mixture was purged with argon and THF (0.6 mL, 0.025 M) was added followed by allyl acetate (6.5 μL, 0.06 mmol, 400 mol %). The resulting mixture was stirred at 100 ℃ for 1 hour. The reaction mixture was then allowed to cool to ambient temperature. Upon flash column chromatography (SiO_2, 30-50% Et_2O:pentane), the title catalyst Ir-PP-I (7.8 mg, 0.009 mmol,) was obtained as a yellow powder in 60% yield.

R_f = 0.45 (1:1 hexanes : EtOAc)

^{31}P NMR (162 MHz, C_6D_6) δ: -64.1, -10.3.

HRMS (ESI [M-Cl]+, *m/z*) for $C_{42}H_{36}IrO_2P_2$: calcd. = 827.1817; found = 827.1818.

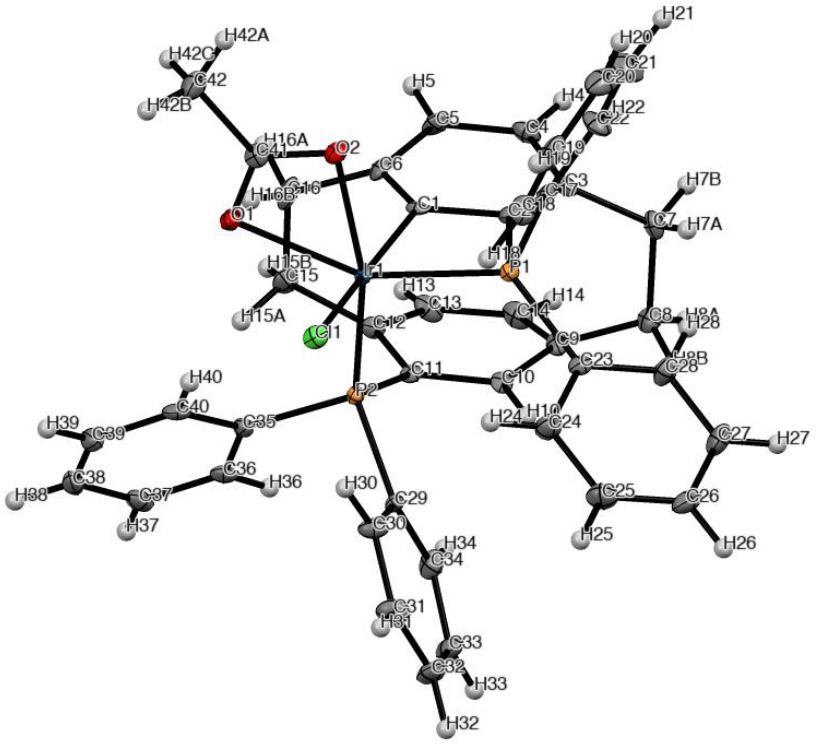

-10.37
-64.08
Me
O
O
Ir
PPh2
Cl
Ph2P
Ir-PP-I
31P (162 MHz, C6D6)
50 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -25
f1 (ppm)

2.5.4.8 Single Crystal Diffraction Data for Ir-PP-I

Single Crystal Diffraction Data for Ir-PP-I

Empirical formula	C43 H38 Cl3 Ir O2 P2	
Formula weight	947.22	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 12.012(2) Å	□= 90°.
	b = 15.314(2) Å	□= 90°.
	c = 20.235(3) Å	□ = 90°.
Volume	3722.3(10) $Å^3$	
Z	4	
Density (calculated)	1.690 Mg/m^3	
Absorption coefficient	3.926 mm^{-1}	
F(000)	1880	
Crystal size	0.170 x 0.060 x 0.050 mm^3	
Theta range for data collection	2.013 to 28.380°.	
Index ranges	-16<=h<=16, -20<=k<=20, -26<=l<=27	
Reflections collected	77190	
Independent reflections	9295 [R(int) = 0.0796]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	0.8476 and 0.5258	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9295 / 306 / 461	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0266, wR2 = 0.0571	
R indices (all data)	R1 = 0.0319, wR2 = 0.0584	
Absolute structure parameter	-0.008(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.390 and -0.734 $e.Å^{-3}$	

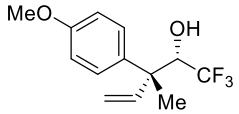
Figure 2.10 Crystal Structure of Ir-PP-I



View of Ir-PP-I showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

2.5.4.9 Procedures and Spectral Data for the Coupling Products Utilzing Ir-PP-I

(2*S*,3*R*)-1,1,1-trifluoro-3-(4-methoxyphenyl)-3-methylpent-4-en-2-ol (2.8e)

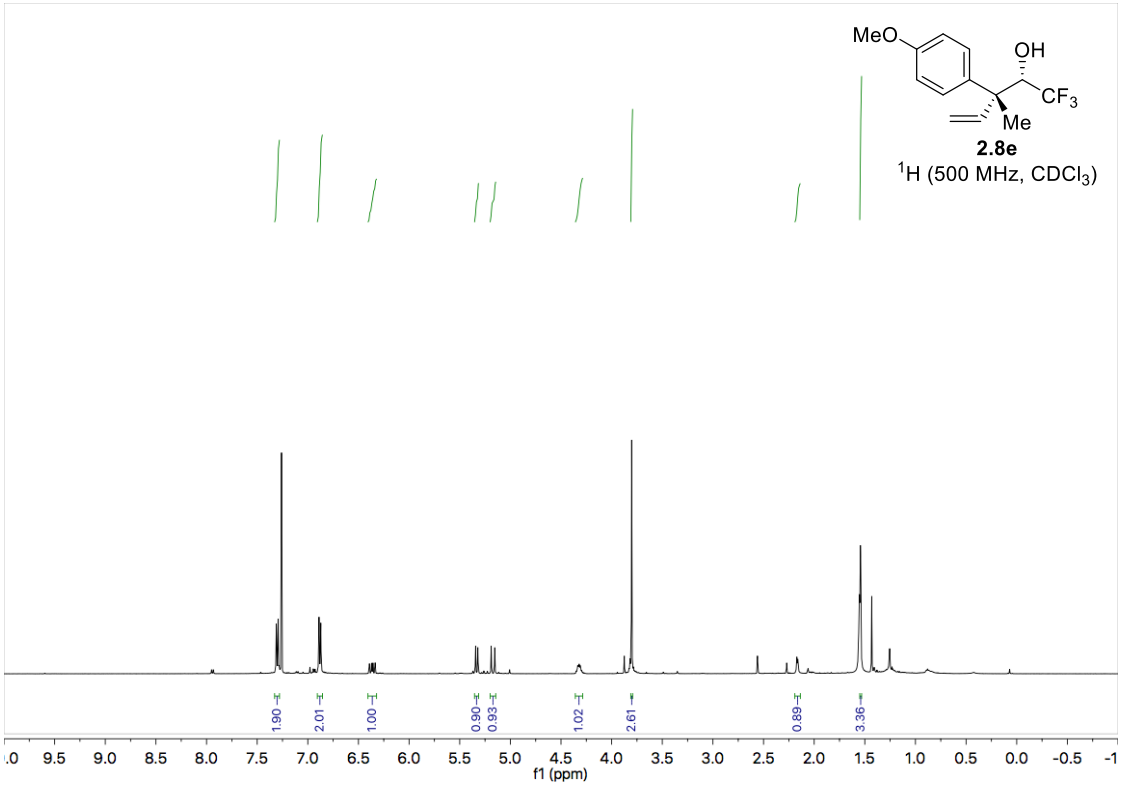


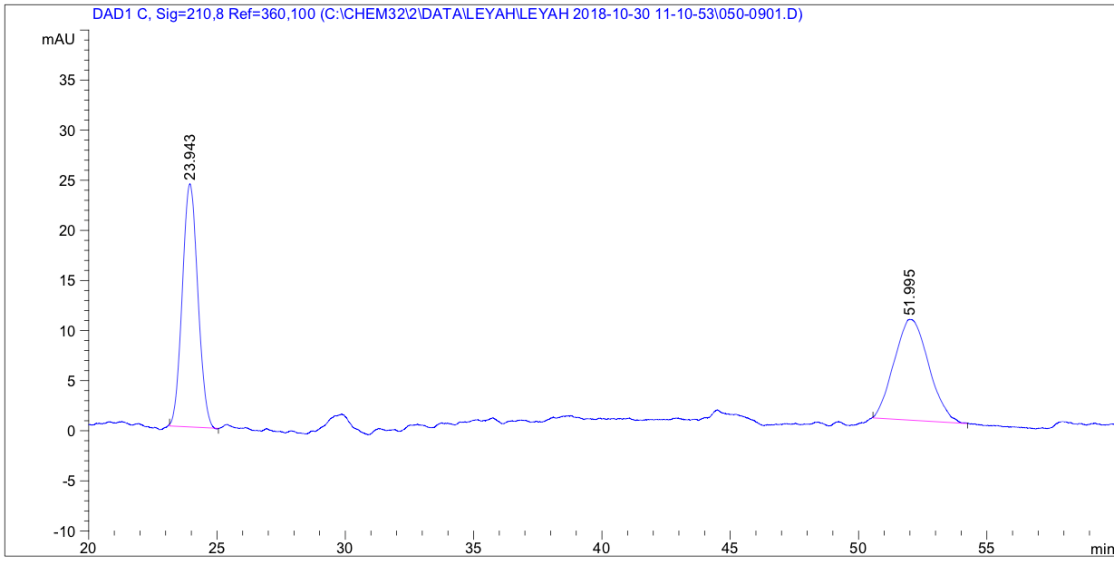
2.8e

To a dried pressure tube under an argon atmosphere charged with Ir-PP-**I** (8.6 mg, 0.01 mmol, 5 mol%), tetrabutylammonium chloride (56.5 mg, 0.2 mmol, 100 mol%) and dried 4 Å molecular sieves (90 mg, 300 wt%) was added 1,1-disubstituted allene **2.6e** (64.1 mg, 0.4 mmol, 200 mol%), isopropanol (200 mol%) and tert-butanol (0.2M) followed by fluoral hydrate (30.9 mg, 0.2 mmol, 100 mol%). The reaction mixture was allowed to stir for 16 hours at 100 °C. The solvent was removed *in vacuo*. Upon flash column chromatography (SiO_2, 5:95 EtOAc:hexanes), the title compound **2.8e** (37.3 mg, 0.14 mmol, 14:1 dr) was obtained as a light yellow oil in 72% yield.

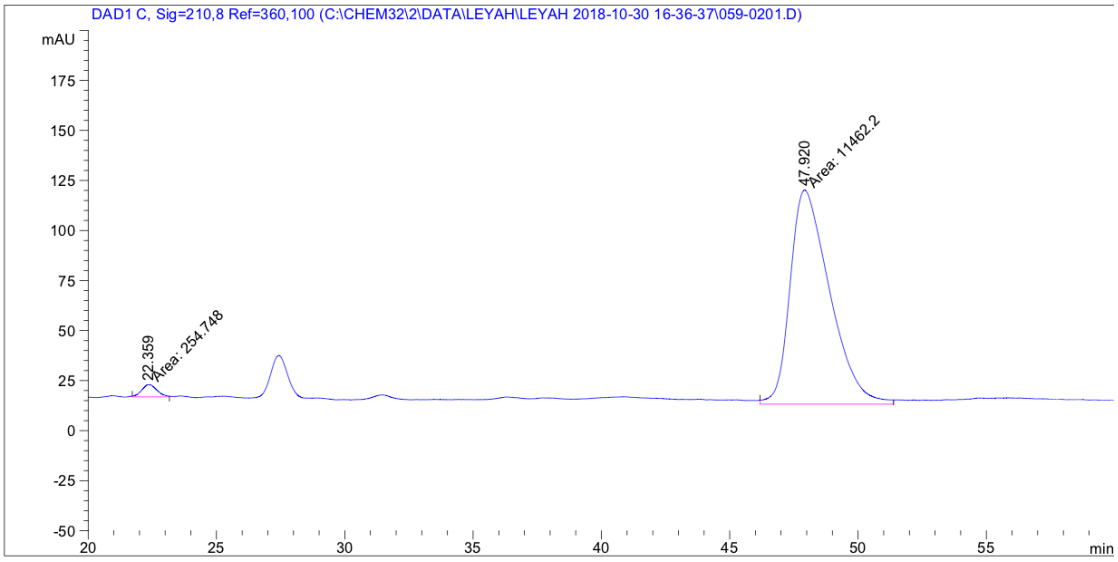
The data collected on this sample was in total agreement with the data collected above with the use of *in situ* generated catalyst to form **2.8e**.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 92:8, 1.0 mL/min, 210 nm) ee = 96%.


MeO
OH
CF3
Me
2.8e
1H (500 MHz, CDCl3)
1.90
2.01
1.00
0.90
0.93
1.02
2.61
0.89
3.36
f1 (ppm)

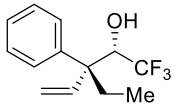


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.943	BB	0.6220	1023.28094	24.26306	52.0288
2	51.995	BB	1.1013	943.47607	10.04927	47.9712



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.359	MM	0.6910	254.74832	6.14480	2.1742
2	47.920	MM	1.7866	1.14622e4	106.92553	97.8258

(2*S*,3*R*)-3-ethyl-1,1,1-trifluoro-3-phenylpent-4-en-2-ol (2.8p)

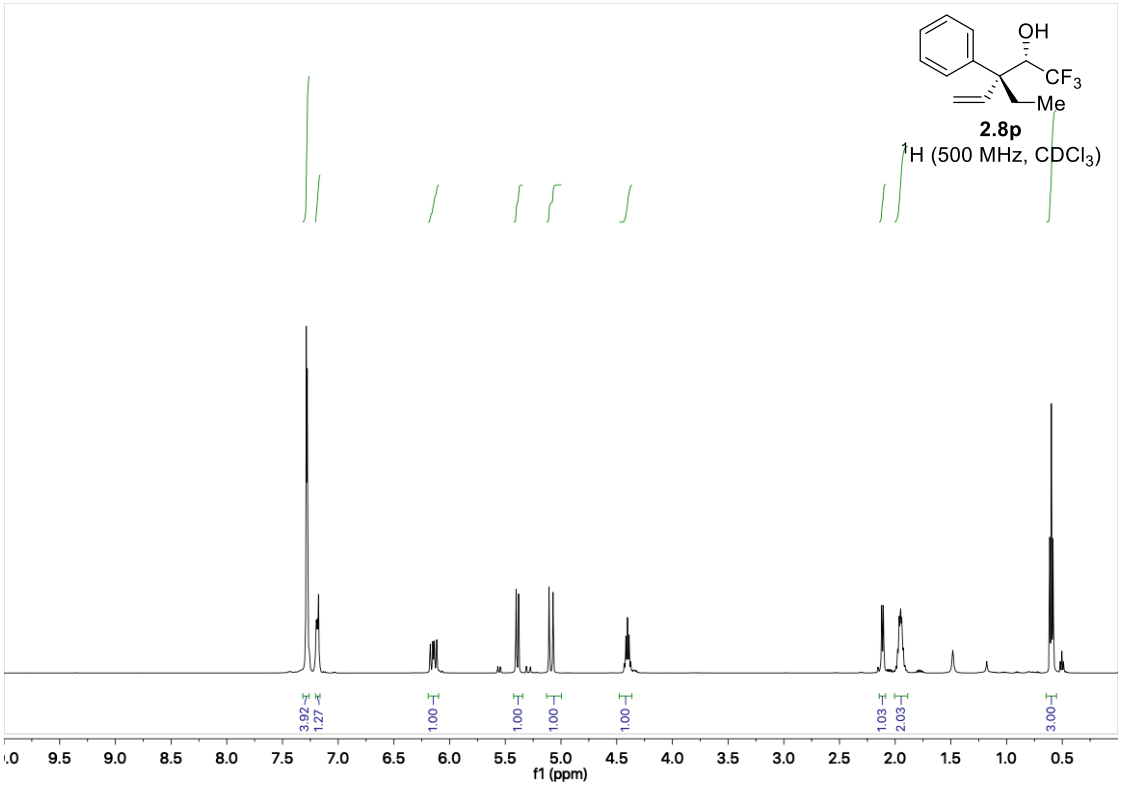


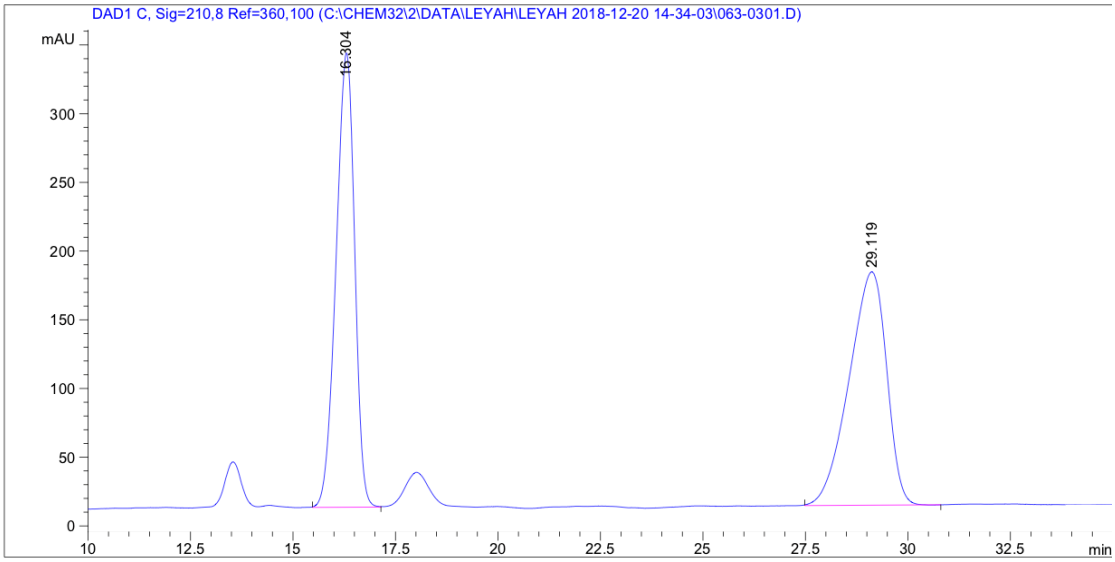
2.8p

To a dried pressure tube under an argon atmosphere charged with Ir-PP-**I** (8.6 mg, 0.01 mmol, 5 mol%), tetrabutylammonium chloride (56.5 mg, 0.2 mmol, 100 mol%) and dried 4 Å molecular sieves (90 mg, 300 wt%) was added 1,1-disubstituted allene **2.6p** (57.7 mg, 0.4 mmol, 200 mol%), isopropanol (200 mol%) and tert-butanol (0.2M) followed by fluoral hydrate (30.9 mg, 0.2 mmol, 100 mol%). The reaction mixture was allowed to stir for 16 hours at 100 °C. The solvent was removed *in vacuo*. Upon flash column chromatography (SiO_2, 4:96 EtOAc:hexanes), the title compound **2.8p** (30.3 mg, 0.12 mmol, 16:1 dr) was obtained as a yellow oil in 62% yield.

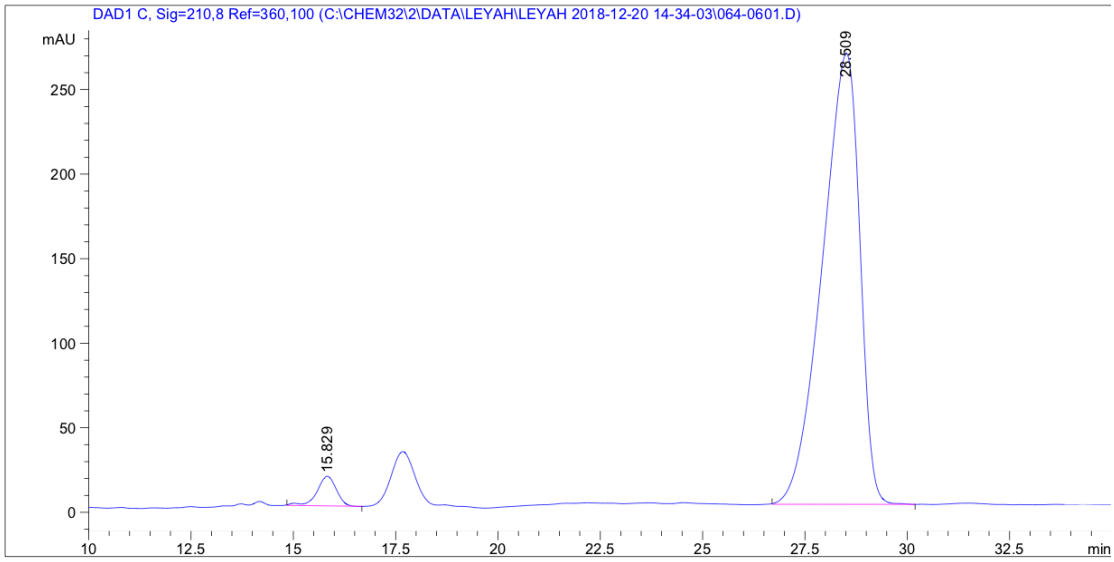
The data collected on this sample was in total agreement with the data collected above with the use of *in situ* generated catalyst to form **2.8p**.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 93%.


OH
CF3
Me
2.8p
1H (500 MHz, CDCl3)
3.92
1.27
1.00
1.00
1.00
1.00
1.03
2.03
3.00
f1 (ppm)

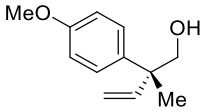


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.304	BB	0.4944	1.04379e4	330.59106	49.1644
2	29.119	BB	0.9617	1.07927e4	169.77098	50.8356



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.829	BB	0.4912	576.09253	17.54015	3.2929
2	28.509	BB	0.9641	1.69188e4	266.71353	96.7071

(*R*)-2-(4-methoxyphenyl)-2-methylbut-3-en-1-ol (2.12)

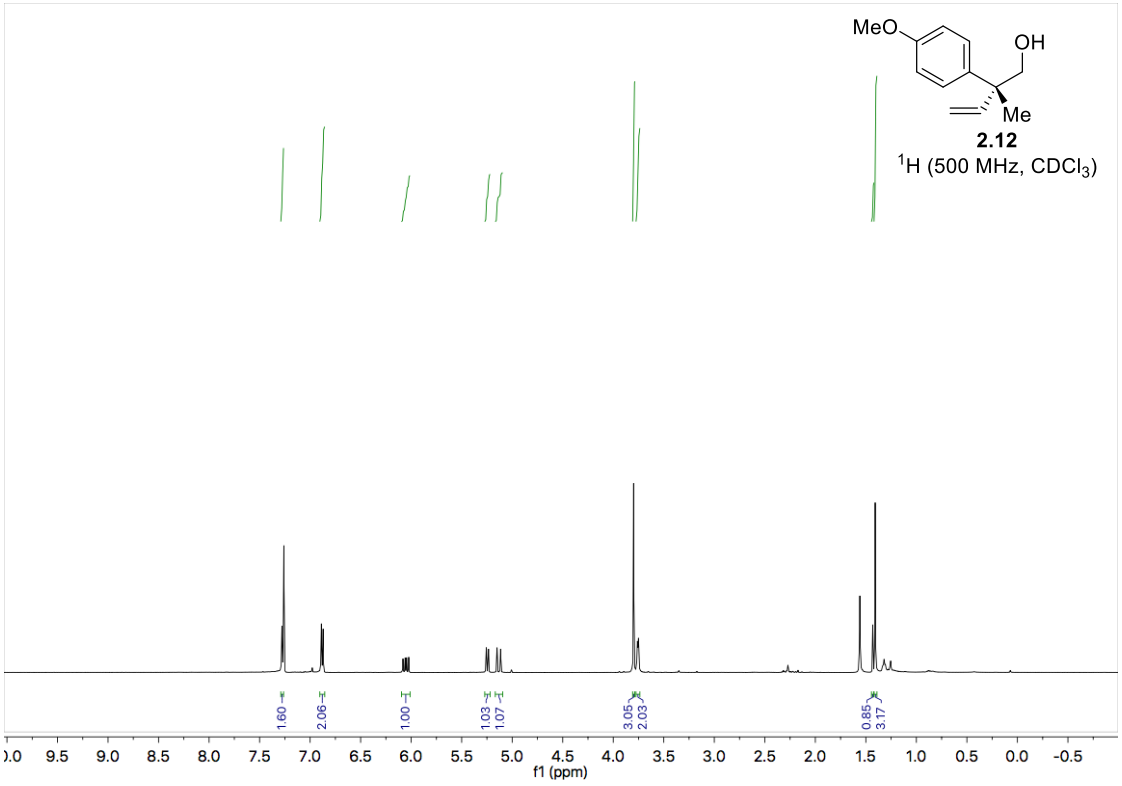


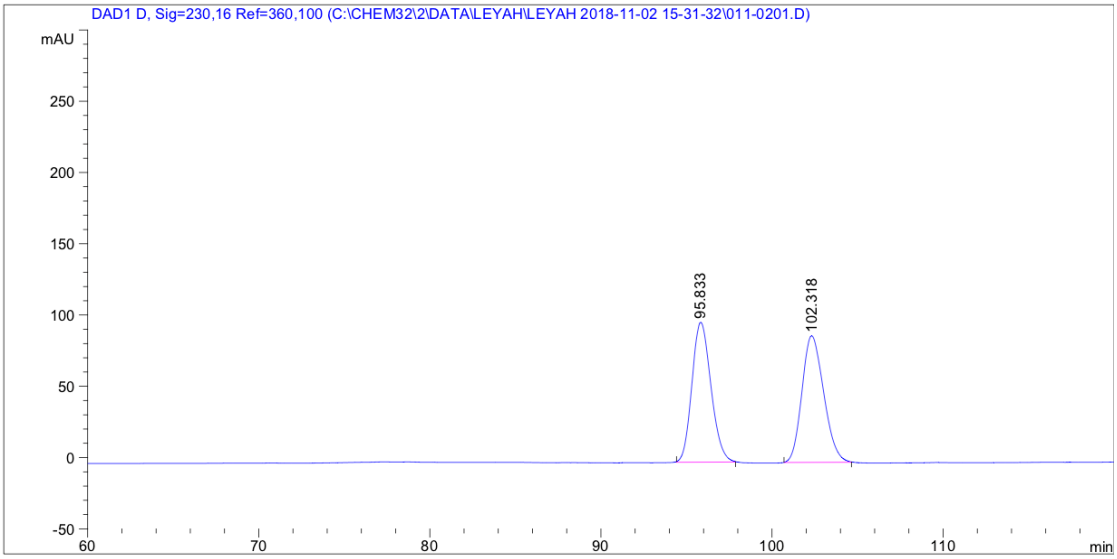
2.12

To a dried pressure tube under an argon atmosphere charged with Ir-PP-**I** (8.6 mg, 0.01 mmol, 5 mol%) was added diene *iso*-**2.6e** (32.0 mg, 0.2 mmol, 100 mol%), methanol (0.2 mL, 1 M), and acetone (2 mL, 0.1 M). The reaction mixture was allowed to stir for 48 hours at 80 °C. The solvent was removed *in vacuo*. Upon flash column chromatography (SiO_2, 1:5 EtOAc:hexanes), the title compound **2.12** (19.3 mg, 0.10 mmol) was obtained as a clear oil in 50% yield.

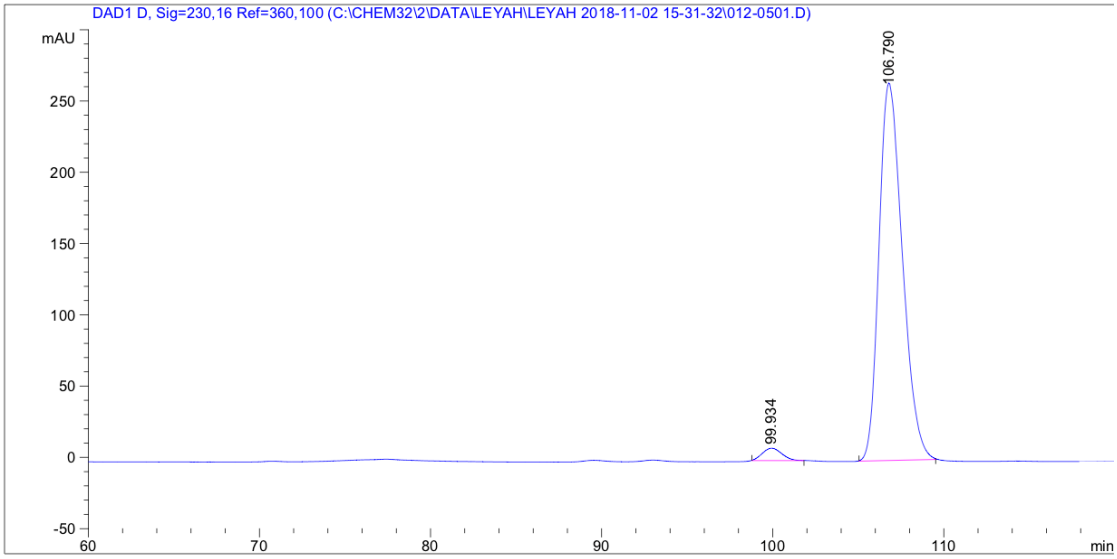
The data collected on this sample was in total agreement with the literature data collected previously with the use of *in situ* generated catalyst.[3c]

HPLC: (Chiralcel column AD-H x2, Hexane:2-PrOH = 98:2, 0.5 mL/min, 230 nm) ee = 95%.


MeO
OH
Me
2.12
^{1}H (500 MHz, CDCl$_3$)
1.60
2.06
1.00
1.03
1.07
3.05
2.03
0.85
3.17
f1 (ppm)

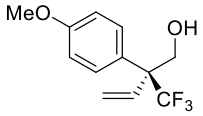


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	95.833	BB	1.1786	7590.77441	98.12029	49.1375
2	102.318	BB	1.3601	7857.24756	88.81841	50.8625



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	99.934	BB	0.9236	682.62646	8.66064	2.6387
2	106.790	BB	1.4601	2.51872e4	264.69504	97.3613

(*S*)-2-(4-methoxyphenyl)-2-(trifluoromethyl)but-3-en-1-ol (2.2d)

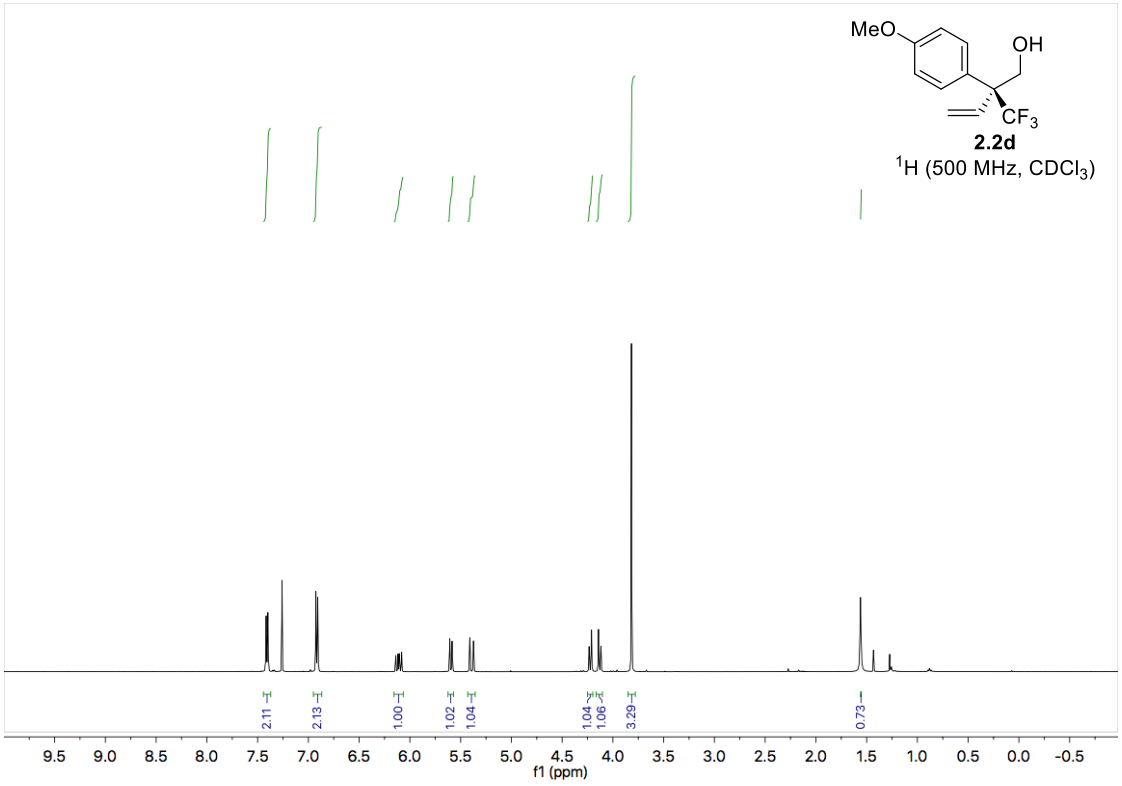


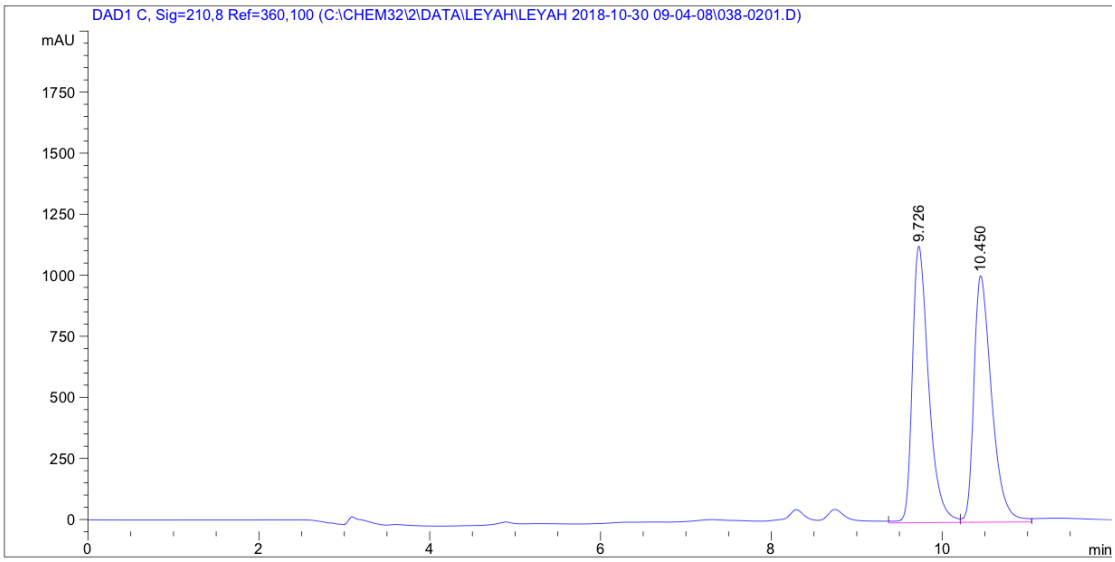
2.2d

To a dried pressure tube under an argon atmosphere charged with Ir-PP-**I** (8.6 mg, 0.01 mmol, 5 mol%) and tetrabutylammonium iodide (6.4 mg, 0.02 mmol, 10 mol%) was added allene **2.1d** (42.8 mg, 0.2 mmol, 100 mol%), methanol (0.2 mL, 1 M) and acetone (2 mL, 0.1 M). The reaction mixture was allowed to stir for 18 hours at 70 °C. The solvent was removed *in vacuo*. Upon flash column chromatography (SiO_2, 15:85 EtOAc:hexanes), the title compound **2.2d** (42.5 mg, 0.17 mmol) was obtained as a clear oil in 86% yield.

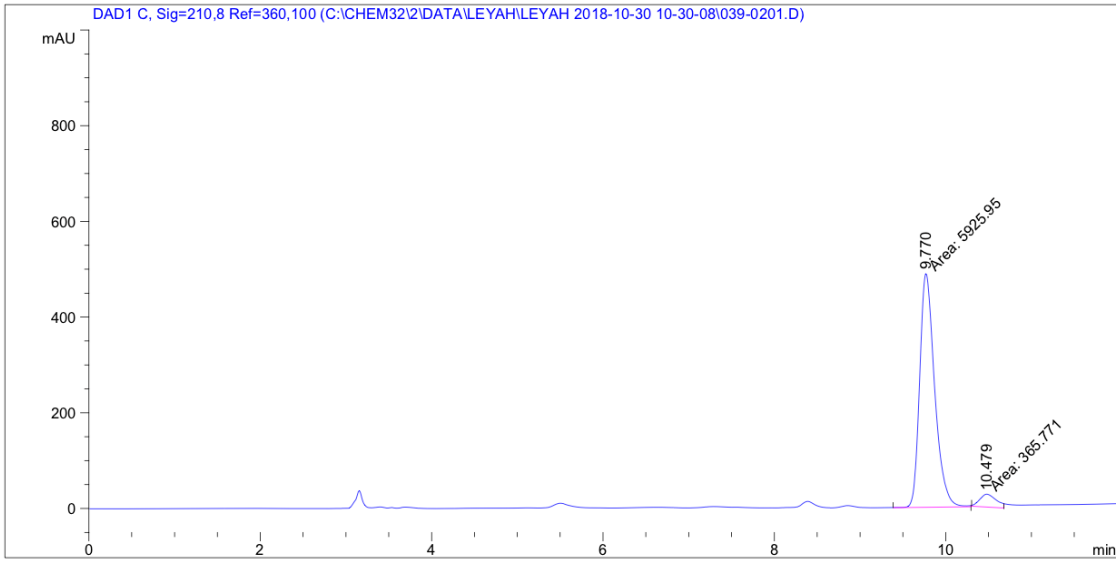
The data collected on this sample was in total agreement with the literature data collected previously with the use of *in situ* generated catalyst.[22]

HPLC: (Chiralcel column OD-3, Hexane:2-PrOH = 95:5, 1.0 mL/min, 210 nm) ee = 88%.


MeO
OH
CF3
2.2d
1H (500 MHz, CDCl3)
2.11
2.13
1.00
1.02
1.04
1.04
1.06
3.29
0.73
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.726	VV	0.2031	1.50542e4	1132.36816	50.6871
2	10.450	VV	0.2211	1.46460e4	1010.17102	49.3129



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.770	MM	0.2021	5925.94824	488.69601	94.1865
2	10.479	MM	0.2265	365.77054	26.91093	5.8135

2.5.4.10 Kinetic Studies

Standard Conditions: To a dried 10 mL volumetric flask under an argon atmosphere charged with $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol, 2.5 mol%), (*R*)-PhanePhos (28.8 mg, 0.05 mmol, 5 mol%) and tetrabutylammonium chloride (277.9 mg, 1 mmol, 100 mol%) was added 1,1-disubstituted allene (260.4, 2 mmol, 200 mol%), isopropanol (0.15 mL, 2 mmol, 200 mol%) and fluoral hydrate (154.7 mg, 1 mmol, 100 mol%). The flask was then filled to the mark with tert-butanol and sonicated until full dissolution. To a dried pressure tube under an argon atmosphere charged with dried 4 Å molecular sieves (46 mg) was added 1 mL of the reaction mixture and the tube quickly sealed. Equal number of reaction tubes were assembled per time point monitored. The reaction mixtures were then allowed to stir at 100 °C with a tube removed each hour for analysis.

Reaction progress was monitored by GC analysis. The reaction was cooled to room temperature before 20 μL of cyclodecane (internal standard) was added and then the mixture diluted with dichloromethane (~4 mL). The mixture was then filtered through a small amount of silica gel in a pipette prior to analysis. The concentration of product was determined by GC analysis.

Reaction order determined by submitting data to Bures plot analysis.[38,39]

Table 2.5 Further reaction conditions for the kinetic experiments.

Experiment	[cat] (M)	[allene] (M)	[fluoral] (M)	[excess] [allene]-[fluoral] (M)
Standard	0.005	0.2	0.1	0.1
Different excess 1	0.005	0.4	0.1	0.3
Different excess 2	0.005	0.2	0.2	0.0
Same excess	0.005	0.3	0.2	0.1
Increased catalyst	0.01	0.2	0.1	0.1

Figure 2.11 Product Formation Under Standard Conditions

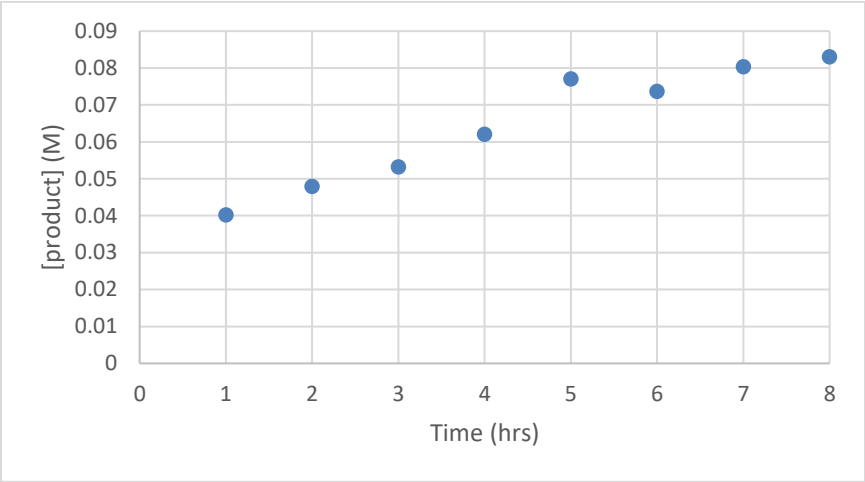


Figure 2.12 Product Formation Under Different Excess 1 Conditions

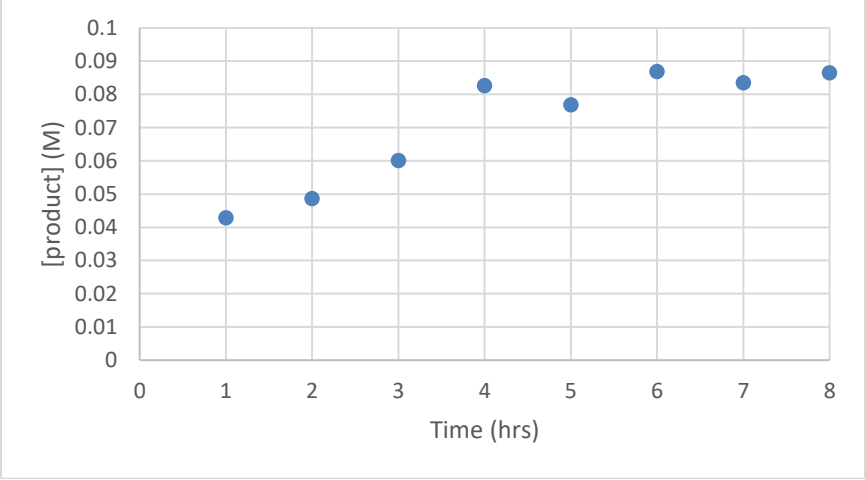


Figure 2.13 Product Formation Under Different Excess 2 Conditions

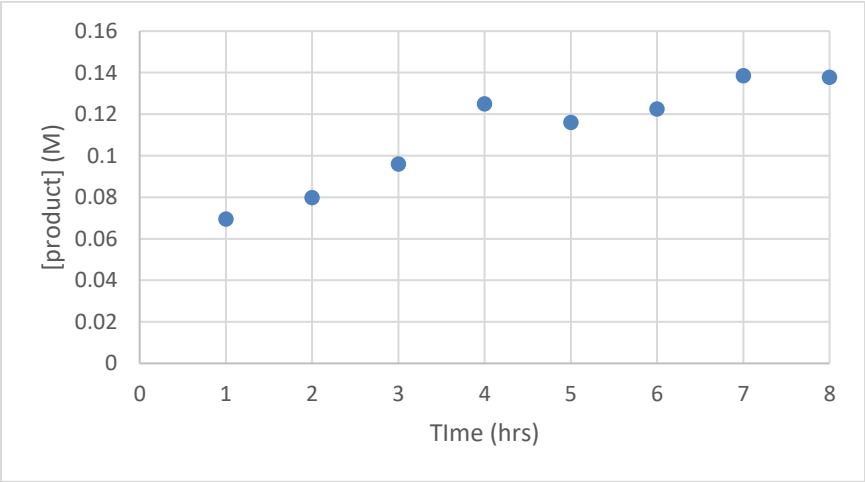


Figure 2.14 Product Formation Under Same Excess Conditions

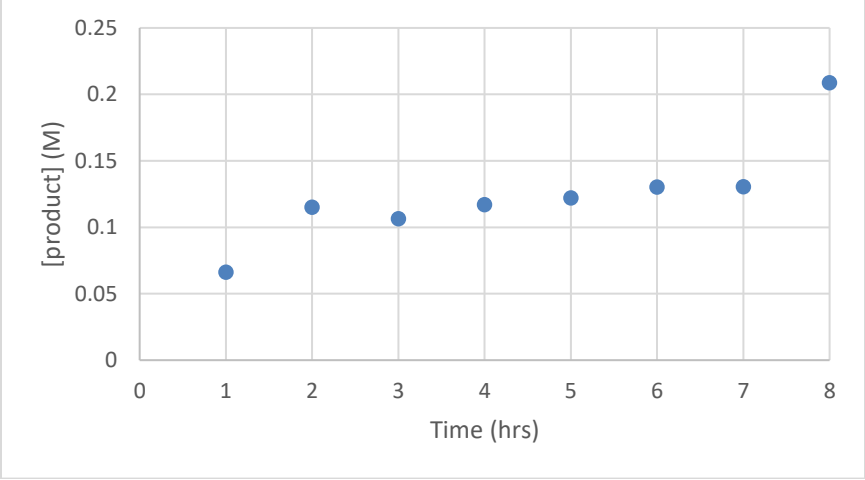
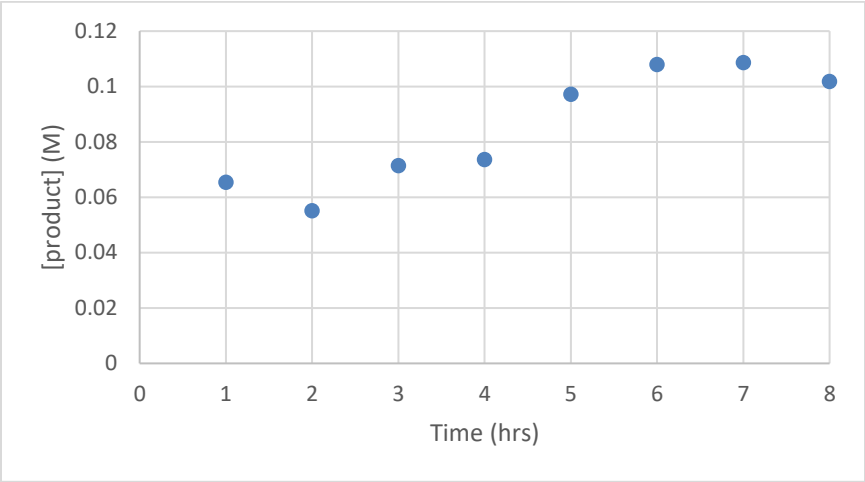
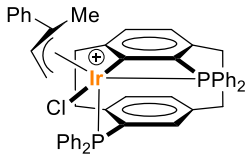


Figure 2.15 Product Formation Under Increased Catalyst Conditions



2.5.4.11 HRMS Identification of Catalytic Intermediate



Chemical Formula: $C_{50}H_{44}IrP_2$
Exact Mass: 899.2547

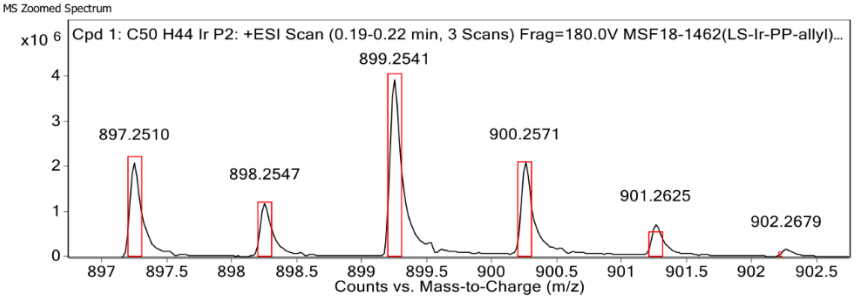
Note: Loss of chloride ion resulting in M+ ion species

Target Compound Screening Report

Results Acquired by The University of Texas at Austin Mass Spectrometry Facility

Data File	MSF18-1462(LS-Ir-PP-allyl)_hrESIpos1.d	**Sample Name**	1462(LS-Ir-PP-allyl)	**Comment**	1462(LS-Ir-PP-allyl)
Position	P1-C2	**Instrument Name**	Instrument 1	**User Name**	
Acq Method	pos.m	**Acquired Time**	12/18/2018 1:31:40 PM	**DA Method**	KS.m

MS Zoomed Spectrum



MS Spectrum Peak List

Obs. m/z	Calc. m/z	Charge	Abundance	Formula	Ion Species	Tgt Mass Error (ppm)
897.2510	897.2519	1	2091959	C50H44IrP2	M+	0.97
898.2547	898.2552	1	1211029	C50H44IrP2	M+	0.62
899.2541	899.2546	1	3946953	C50H44IrP2	M+	0.51
900.2571	900.2577	1	2099741	C50H44IrP2	M+	0.66
901.2625	901.2610	1	729287	C50H44IrP2	M+	-1.61
902.2679	902.2644	1	155926	C50H44IrP2	M+	-3.87
903.2714	903.2678	1	26474	C50H44IrP2	M+	-3.99
904.2724	904.2711	1	4226	C50H44IrP2	M+	-1.43
905.2483	905.2745	1	2875	C50H44IrP2	M+	28.97

--- End Of Report ---

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Chapter 3: Direction Conversion of Primary Alcohols to 1,2-Amino Alcohols: Enantioselective Irdium-Catalyzed Carbonyl Reductive Coupling of Phthalimido-Allene via Hydrogen Auto-Transfer*

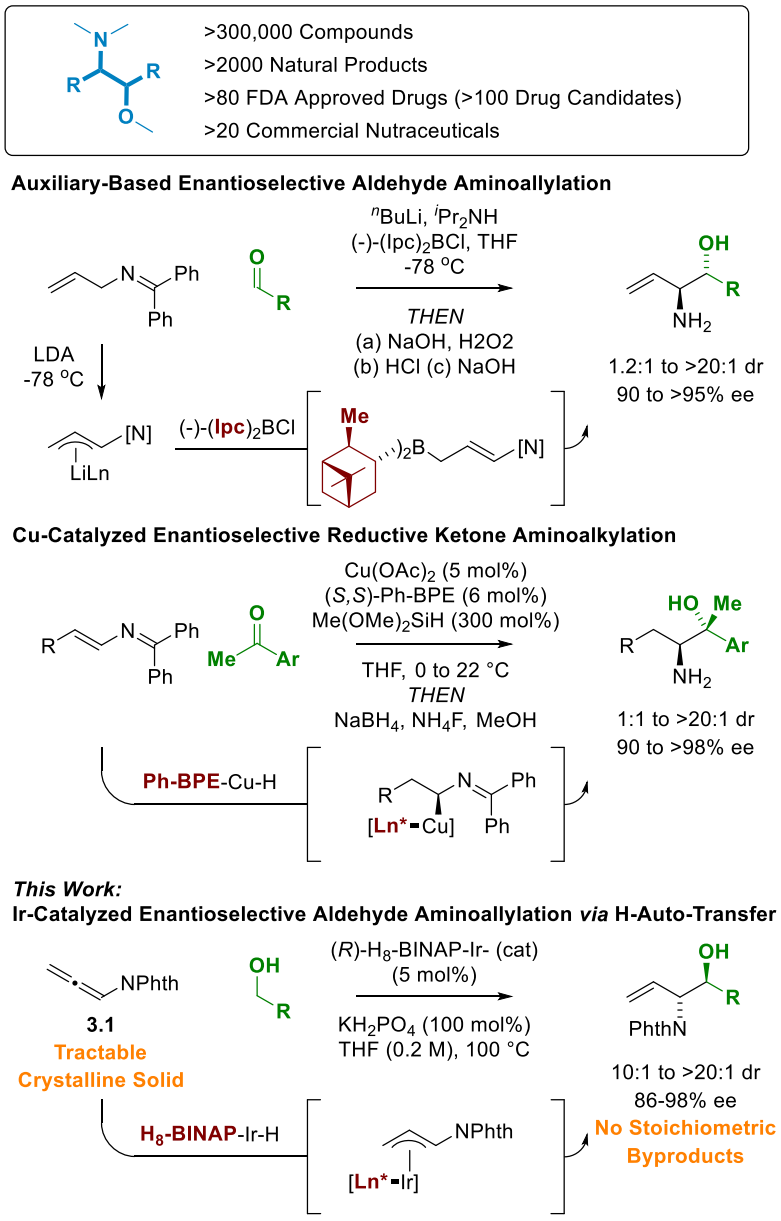
3.1 INTRODUCTION

Asymmetric carbonyl addition ranks foremost among methods used for the convergent construction of enantiomerically enriched alcohols.[1] Data mining of patents from the pharmaceutical industry reveals that carbonyl addition (alongside Suzuki coupling) remains one of the most frequently utilized methods for C–C bond formation.[2] The vast majority of carbonyl addition reactions rely on the use of preformed carbanions, which can be moisture sensitive, unsafe, and often require multi-step preparation and cryogenic conditions. Metal-catalyzed carbonyl reductive coupling of π-unsaturated pronucleophiles has emerged as an alternative to the use of stoichiometric carbanions.[3] However, many of the terminal reductants utilized in such processes (e.g., Mn, Zn, Et_3B, Et_2Zn) are as problematic as the premetalated reagents they replace. Carbonyl reductive coupling via hydrogen auto-transfer does not require an exogenous reductant, as alcohol reactants serve dually as reductant and carbonyl proelectrophile.[4]

Based on this concept and motivated by the prevalence (>40%) of chiral amines (including vicinal amino alcohols) in FDA-approved drugs,[5a,b] a catalytic enantioselective carbonyl (α-amino)allylation was sought.[6–8] In 1993, Barrett reported a boron reagent for asymmetric carbonyl (α-amino)allylation.[7] Remarkably, after more than 25 years, corresponding catalytic enantioselective processes have remained elusive, and the only

* This chapter is based on the previously published work:
Spielmann, K.; Xiang, M.; Schwartz, L. A.; Krische, M. J. Direct Conversion of Primary Alcohols to 1,2-Amino Alcohols: Enantioselective Iridium-Catalyzed Carbonyl Reductive Coupling of Phthalimido-Allene via Hydrogen Auto-Transfer. *J. Am. Chem. Soc.* **2019**, *141*, 14136.
L.A.S. contributed to reaction discovery and optimization (Table 3.1), substrate scope (Tables 3.2A & B), kinetic and mechanistic studies (Figures 3.2, 3.2, and 3.7–3.17; Schemes 3.2 and 3.3), and preparation of manuscript and supporting information.

Figure 3.1 Selected Enantioselective Methods for Convergent Construction of Vicinal Amino Alcohols via Classical and Metal-Catalyzed Carbonyl Addition



related catalytic transformation to have appeared is the 2-azadiene-ketone reductive coupling reported by Malcolmson.[9] Phthalimido-allene **3.1**, a tractable crystalline solid (mp = 79−81 °C), participates in catalytic enantioselective carbonyl reductive coupling via hydrogen autotransfer to deliver vicinal amino alcohols with high levels of regio-, anti-

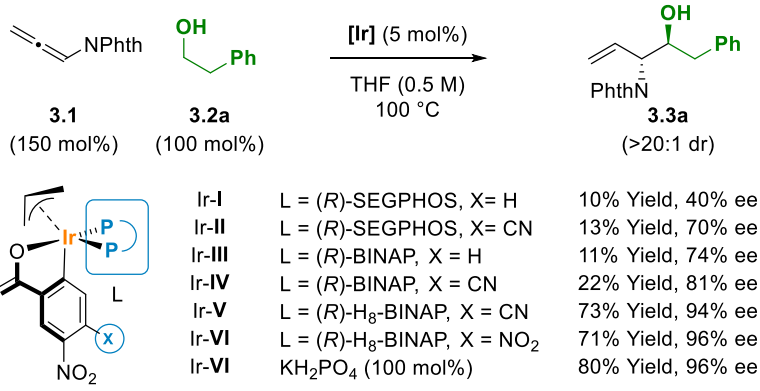
diastereo-, and enantiocontrol (Figure 3.1). This represents a rare example of the use of allene pronucleophiles in enantioselective carbonyl reductive coupling.[10]

3.2 Reaction Development and Scope

Phthalimido allene **3.1** is readily prepared through base-catalyzed isomerization of commercially available *N*-propargyl phthalimide.[11] Guided by seminal findings from the Krische laboratory,[12] it was posited that hydrogen transfer from primary alcohols to allenimide **3.1** would generate transient (phthalimido)allyliridium–aldehyde pairs that combine by way of closed six-centered transition structures to furnish *anti*-vicinal amino alcohols. The feasibility of this transformation was rendered uncertain by competing conventional transfer hydrogenation of allene **3.1** in response to the steric demand of the phthalimide moiety, which may retard the rate of aldehyde addition. An assay of diverse chiral ruthenium and iridium complexes was undertaken, and a promising result was obtained using the cyclometalated π-allyliridium complex modified by 3-nitrobenzoic acid and (*R*)-SEGPHOS, Ir-**I**, which delivered the desired amino alcohol **3.3a** in 10% yield and 40% ee with >20:1 *anti*-diastereoselectivity (Table 3.1). Enantioselectivity improved using the more Lewis acidic 4-cyano-3-nitro-*C,O*-benzoate, Ir-**II**, but the isolated yield of **3.3a** remained modest due to low conversion. Similar trends were observed with the corresponding catalysts based on (*R*)-BINAP, Ir-**III** and Ir-**IV**, but with a small increase in enantioselectivity. A pronounced improvement in both conversion and enantioselectivity was observed upon use of Ir-**V**, which incorporates (*R*)-H_8-BINAP.[13] Use of the (*R*)-H_8-BINAP iridium complex bound by 3,4-dinitro-*C,O*-benzoic acid, Ir-**VI**, provided still higher levels of enantioselectivity. Finally, introduction of monobasic potassium phosphate led to higher conversion, allowing **3.3a** to be formed in 80% yield, 96% ee with complete

anti-diastereoselectivity (Table 3.1). As borne out by single-crystal X-ray diffraction analysis of Ir-**VI**, the dihedral angle between the tetralin rings of (*R*)-H_8-BINAP (ca. 86°) is significantly larger than the dihedral angle between the naphthalene rings of BINAP (ca. 75°) or SEGPHOS (ca. 72°),[14] which may better accommodate the sterically demanding phthalimide moiety to facilitate alkoxide exchange at the metal center.

Table 3.1 Selected Optimization Experiments in the Enantioselective Iridium-Catalyzed (α-Amino)allylation of Phthalimido-Allene **3.1** with Alcohol **3.2a**[a]

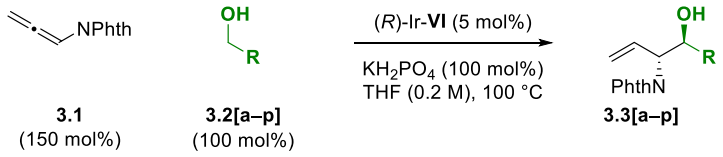


[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase high performance liquid chromatography (HPLC) analysis.

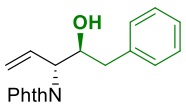
Reaction scope was evaluated by applying optimal conditions identified for the (α-amino)allylation of 2-phenylethanol **3.2a** to diverse alcohols **3.2[b–z, a′–c′]** (Table 3.2A & B). All vicinal amino alcohols **3.3[a–z, a′–c′]** were formed in good yield with excellent levels of diastereo- and enantioselectivity. The (α-amino)allylations of *N*-Boc-ethanolamine **3.2j**, *N*-Boc-propanolamine **3.2k**, and trifluorobutanol **3.2m**, which are commercially available, are significant, as the corresponding aldehydes are not available for purchase and are relatively unstable. Modification of the heteroaryl-containing alcohols **3.2c–i**, **3.2t**, and **3.2u**, which includes perphenazine **3.2g**, an FDA approved drug, establishes the feasibility of utilizing this method for late-stage functionalization.[15] Due to

a pronounced kinetic bias for primary alcohol dehydrogenation,[16] free secondary hydroxyl groups are tolerated, as illustrated in the site-selective formation of (*R*)-butane diol adducts

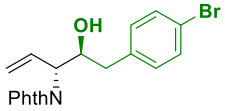
Table 3.2A Diastereo- and Enantioselective Iridium-Catalyzed Hydrohydroxyalkylation of Phthalimido-Allene **3.1** with Alcohols **3.2[a–p]** To Form 1,2-Amino Alcohols **3.3[a–p]**[a]



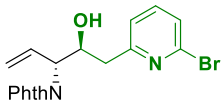
3.1 (150 mol%) | **3.2[a–p]** (100 mol%) | **3.3[a–p]**



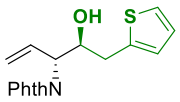
3.3a
80% Yield[b]
>20:1 dr, 96% ee
(X-RAY)



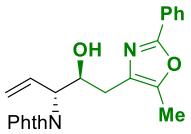
3.3b
65% Yield
>20:1 dr, 97% ee



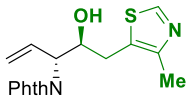
3.3c
61% Yield
>20:1 dr, 96% ee



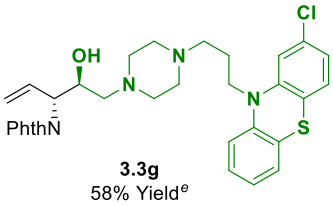
3.3d
67% Yield
>20:1 dr, 92% ee



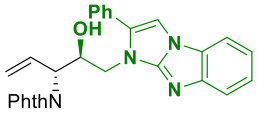
3.3e
71% Yield[e]
>20:1 dr, 96% ee



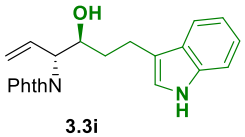
3.3f
72% Yield[c]
>20:1 dr, 94% ee



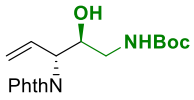
3.3g
58% Yield[e]
>20:1 dr, 98% ee
From Perphenazine



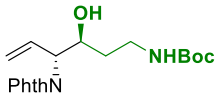
3.3h
57% Yield[e]
>20:1 dr, 98% ee



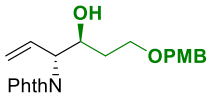
3.3i
75% Yield[e]
>20:1 dr, 96% ee



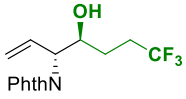
3.3j
66% Yield
>20:1 dr, 97% ee



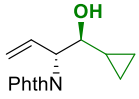
3.3k
60% Yield
>20:1 dr, 94% ee



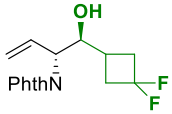
3.3l
71% Yield
>20:1 dr, 97% ee



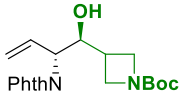
3.3m
75% Yield[e]
>20:1 dr, 96% ee



3.3n
58% Yield[d]
>20:1 dr, 96% ee



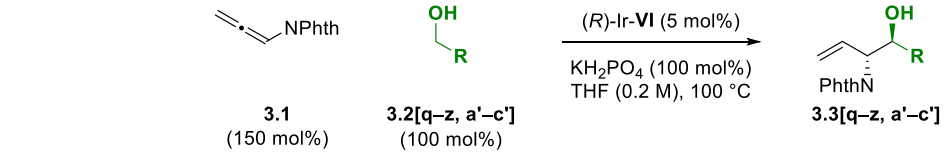
3.3o
61% Yield[c]
>20:1 dr, 94% ee



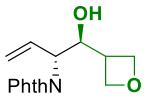
3.3p
67% Yield
>20:1 dr, 97% ee

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Standard conditions: 0.2 mmol scale, 48 h. [b]75%, 1 mmol scale, [c]72 h, [d]Ir-**V**, [e]Ir-**VI** (7.5 mol%).

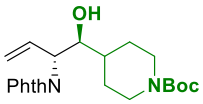
Table 3.2B Diastereo- and Enantioselective Iridium-Catalyzed Hydrohydroxyalkylation of Phthalimido-Allene **3.1** with Alcohols **3.2[q–z, a'–c']** To Form 1,2-Amino Alcohols **3.3[q–z, a'–c']**[a]



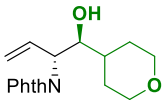
3.1 (150 mol%) | **3.2[q–z, a'–c']** (100 mol%) | **3.3[q–z, a'–c']**



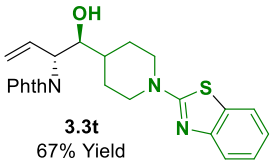
3.3q
79% Yield
>20:1 dr, 96% ee



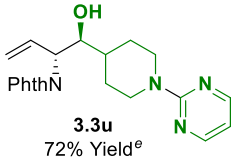
3.3r
70% Yield
>20:1 dr, 93% ee



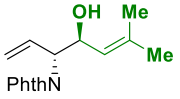
3.3s
79% Yield[e]
>20:1 dr, 94% ee



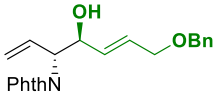
3.3t
67% Yield
>20:1 dr, 94% ee



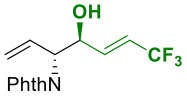
3.3u
72% Yield[e]
>20:1 dr, 95% ee



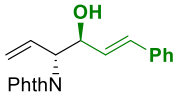
3.3v
70% Yield
>20:1 dr, 86% ee
(X-RAY)



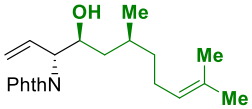
3.3w
69% Yield[e]
>20:1 dr, 88% ee



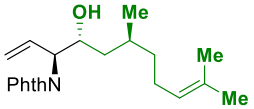
3.3x
61% Yield[e]
>20:1 dr, 90% ee



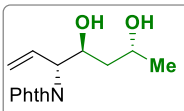
3.3y
73% Yield
>20:1 dr, 86% ee



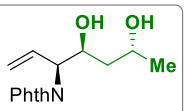
3.3z
62% Yield
10:1 dr



3.3a'
64% Yield, (*S*)-Ir-**VI**
13:1 dr



3.3b'
72% Yield[e]
>20:1 dr



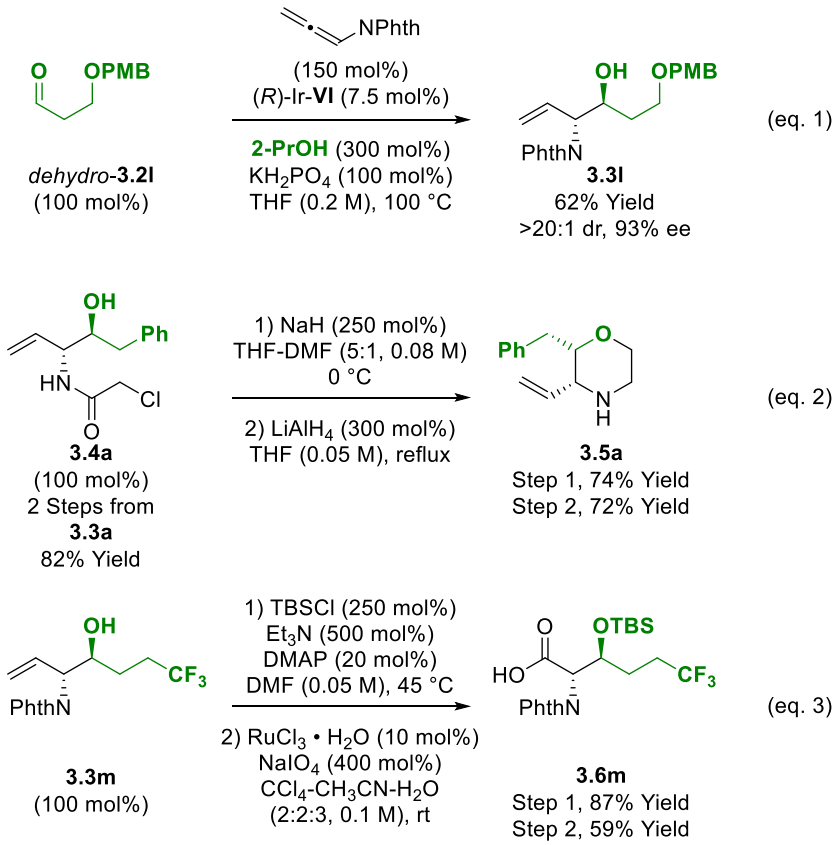
3.3c'
66% Yield[e], (*S*)-Ir-**VI**
>20:1 dr

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Standard conditions: 0.2 mmol scale, 48 h. [b]75%, 1 mmol scale, [c]72 h, [d]Ir-**V**, [e]Ir-**VI** (7.5 mol%).

3.3b′ and **3.3c′**, which occur with complete levels of catalyst-directed diastereoselectivity. Using this first-generation catalytic system, benzylic alcohols are converted to the amino alcohols in high yield but lower enantioselectivities are observed.

As demonstrated by the conversion of *dehydro*-**3.2l** to amino alcohol **3.3l**, the reactions can also be conducted from the aldehyde oxidation level using 2-propanol as terminal reductant (Scheme 3.1, eq. 1). Given the frequent appearance of morpholines as substructures in pharmaceutical ingredients,[17] compound **3.3a** was converted to the morpholine **3.5a** (Scheme 3.1, eq. 2).[18] To further demonstrate utility of amino alcohols **3.3[a−z, a′−c′]**, adduct **3.3m** was subjected to alkene oxidative cleavage to provide the nonproteinogenic amino acid derivative **3.6m** (Scheme 3.1, eq. 3).[19]

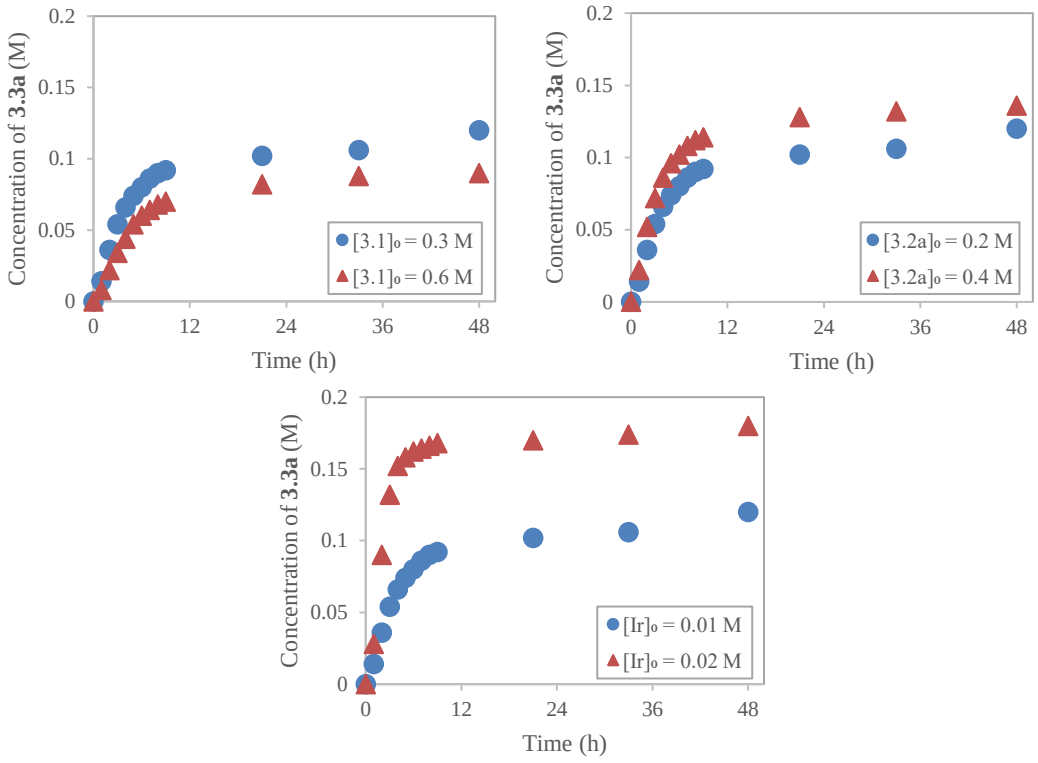
Scheme 3.1 Reactivity From Aldehyde Oxidation Level and Synthesis of Morpholine **3.5a** and Amino Acid Derivative **3.6m**



3.3 Mechanism and Discussion

Reaction progress kinetic analysis (RPKA) using the "different excess" protocol was used to gain mechanistic insight (Figure 3.2).[20] The kinetic order of reactants varied over time; therefore, general trends were evaluated. Doubling the initial concentration of allene **3.1** slightly decreases the rate of product formation. This data suggests allene hydrometalation is rapid, allene **3.1** is not involved in the turnover-limiting step and, at higher concentrations, allene **3.1** inhibits the rate of product formation (Figure 3.2, left).

Figure 3.2 Reaction Progress Kinetic Analysis of the Reductive Coupling of Phthalimido-Allene **3.1** and Alcohol **3.2a**



Product formation as monitored by ^{1}H NMR analysis in reactions conducted using the "different excess" protocol: [Ir] = 0.01 M and [KH_2PO_4] = 0.2 M, with (left) [**3.2a**]$_0$ = 0.2 M, [**3.1**]$_0$ = as noted and (right) [**3.1**]$_0$ = 0.3 M, [**3.2a**]$_0$ = as noted. (Bottom) Product formation as monitored by NMR analysis in reactions with varying catalyst loading: [**3.1**] = 0.3 M, [**3.2a**] = 0.2 M, [KH_2PO_4] = 0.2 M, and [Ir] = as noted.

Doubling the initial concentration of alcohol **3.2a** results in a slight increase in the rate of product formation, signifying a positive order in alcohol **3.2a** (Figure 3.2, right). Increasing the loading of iridium catalyst, (*R*)-Ir-**VI**, results in a dramatic increase in the rate of product formation, demonstrating the reaction is positive order in catalyst (Figure 3.2, bottom). Separate experiments using the "same excess" protocol reveal significant catalyst deactivation that is contributed to by product inhibition.[21] Additionally, introduction of aldehyde *dehydro*-**3.2a** (10 mol%) inhibits product formation, suggesting carbonyl addition may not be turnover limiting.[21]

Deuterium labeling studies provide additional information on the reaction mechanism (Scheme 3.2, eqs 4−6).[22] Exposure of allene **3.1** to *deuterio*-**3.2a** under standard reaction conditions delivers *deuterio*-**3.3a** (Scheme 3.2, eq. 4). Deuterium is completely retained at the carbinol position, suggesting *deuterio*-**3.3a** is inert with respect to dehydrogenation. Incorporation of deuterium at both the internal and terminal vinylic positions corroborates reversible allene hydrometalation with incomplete regioselectivity. In a competition kinetics experiment, allene **3.1** was exposed to equimolar quantities of alcohol **3.2a** and *deuterio*-**3.2a** (Scheme 3.2, eq. 5). The observed levels of deuterium incorporation at the carbinol position of *deuterio*-**3.3a** are consistent with a normal primary kinetic isotope effect ($k_H/k_D \approx 2.3$). Evaluation of the initial rates for the reaction of both **3.2a** and *deuterio*-**3.2a** also reveals a primary kinetic isotope effect ($k_H/k_D \approx 1.5$) (Figure 3.3). Along with the reaction orders suggested from the RPKA experiments, this kinetic isotope effect data was consistent with two scenarios: (1) reversible alcohol dehydrogenation followed by rate-determining carbonyl addition, or (2) rate-determining alcohol dehydrogenation.[22] To determine which of these processes is operative an additional experiment was undertaken (Scheme 3.2, eq. 6). When pthalimido-allene **3.1** is exposed to equimolar quantities of *deuterio*-**3.2a** and *dehydro*-**3.2l** under standard

conditions, hydrogen–deuterium exchange is not observed at the carbinol position of *deuterio*-**3.3a** and *dehydro*-**3.3l**, suggesting alcohol–aldehyde redox equilibration does not occur in advance of carbonyl addition. Hence, the collective data implicate turnover-limiting alcohol dehydrogenation followed by rapid allene hydrometalation.

Scheme 3.2 Deuterium Labeling Studies for the Reductive Coupling of Phthalimido-Allene **3.1** with Alcohols to Form 1,2-Amino Alcohols

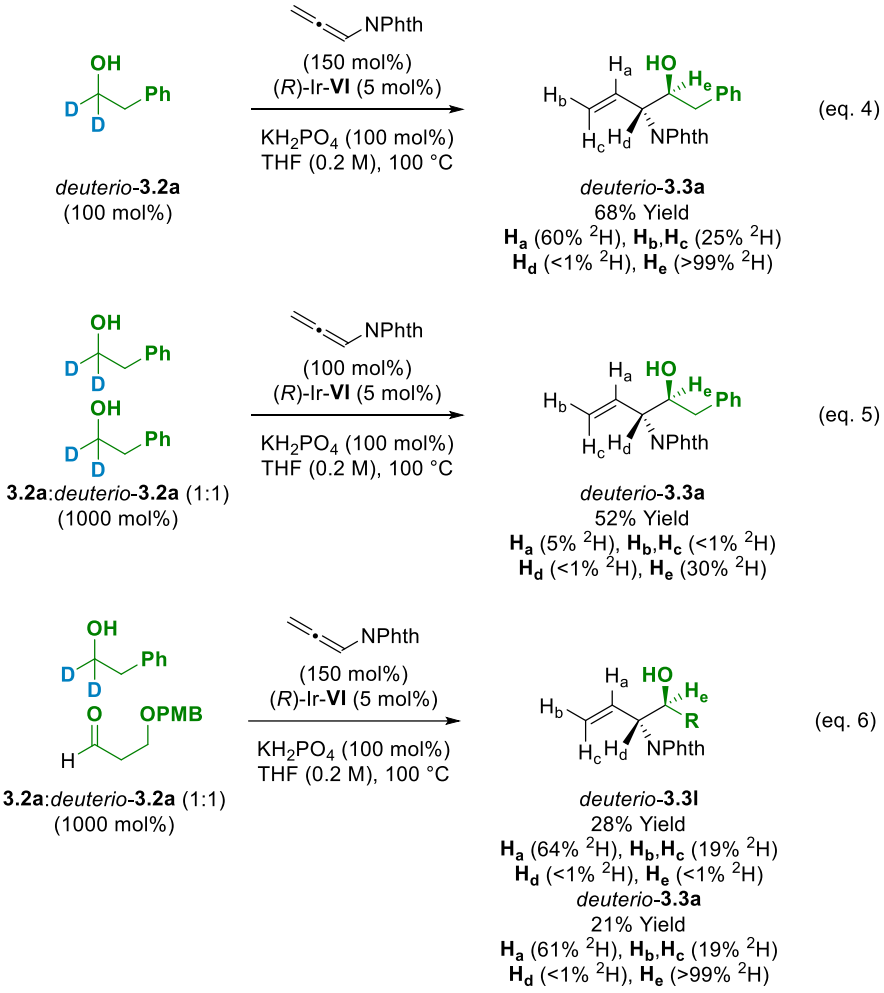
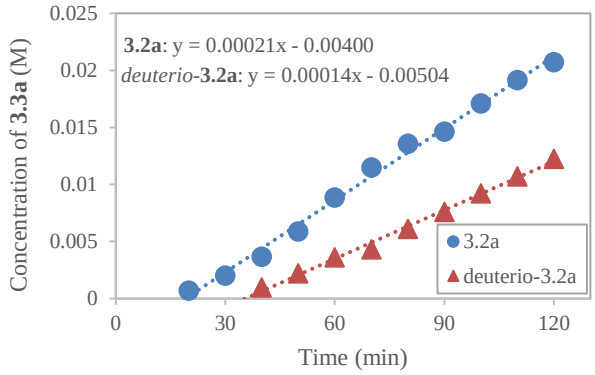


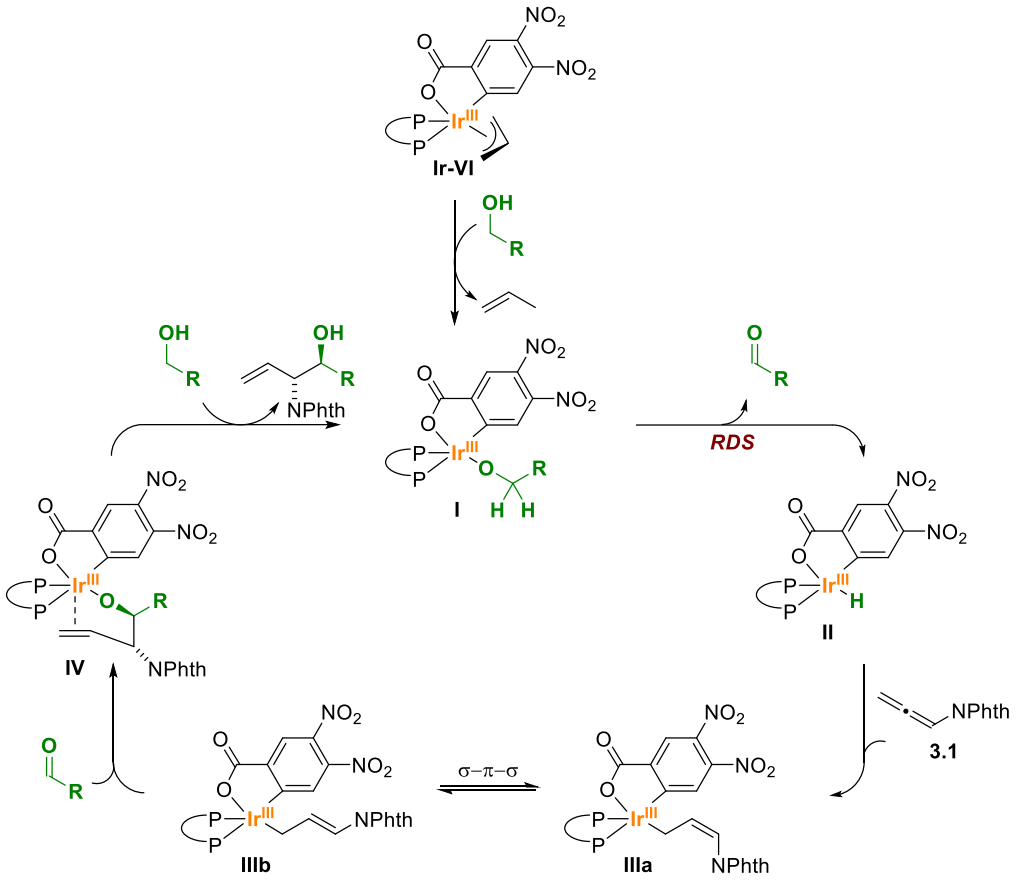
Figure 3.3 Initial Rates Study for Reductive Coupling of Phthalimido-Allene 3.1 with Alcohols **3.2a** and *deuterio*-**3.2a**



Initial Rates Study: [**3.1**]$_0$ = 0.3 M; [**3.2a**]$_0$ or [*deuterio*-**3.2a**]$_0$ = 0.2 M; [Ir] = 0.01 M

Based on the kinetic and isotopic labeling studies, the indicated catalytic mechanism is proposed (Scheme 3.3). Entry into the catalytic cycle occurs through protonolysis of the allyliridium complex (*R*)-Ir-**VI** by the reactant alcohol. The resulting iridium alkoxide **I** undergoes irreversible dehydrogenation to form the iridium hydride **II**, which is rapidly consumed by reversible allene hydrometalation. Due to the steric demand of the phthalimide moiety, the (*Z*)-σ-(amino)allyliridium complex **IIIa** is anticipated to be the kinetic product of allene hydrometalation. Isomerization to the thermodynamically preferred (*E*)-σ-allyliridium complex **IIIb** is followed by aldehyde coordination and carbonyl addition through a closed chair-like transition structure to form iridium(III) alkoxide **IV**. Exchange with the primary alcohol reactant releases product and regenerates iridium alkoxide **I** to close the catalytic cycle.

Scheme 3.3 General Catalytic Mechanism As Corroborated by Kinetic and Isotopic Labeling Studies



3.4 CONCLUSION

In conclusion, a catalytic method for the direct conversion of primary alcohols to vicinal amino alcohols that occurs with high levels of regio-, *anti*-diastereo-, and enantioselectivity has been achieved. This hydrogen auto-transfer process exploits the tractable, crystalline phthalimido-allene **3.1** as pronucleophile and represents the first protocol for catalytic enantioselective carbonyl (α-amino)allylation. More broadly, this work contributes to an evolution from use of traditional carbonyl addition methods that exploit preformed carbanions to byproduct-free catalytic carbonyl reductive couplings, where alcohol proelectrophiles and π-unsaturated pronucleophiles combine by way of transient organometallics.[4]

3.5 EXPERIMENTAL DETAILS

3.5.1 General Information

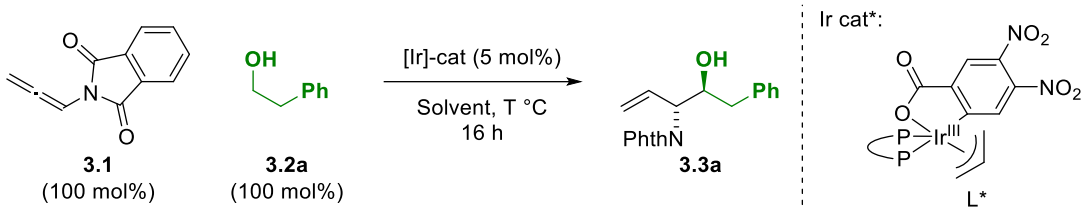
All reactions were run under an atmosphere of argon, unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator or under a stream of argon prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Strem Chemicals, Fischer Scientific, Sigma Aldrich and Combi Blocks) without further purification. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[23] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F254). Visualization was accomplished with UV light followed by dipping in CAM, *p*-Anisaldehyde (PAA), or $KMnO_4$ stain solution followed by heating. Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$. Solution concentrations are given in the units of 10^{-2} g mL^{-1}. Racemic reactions were conducted using racemic catalyst prepared in utilizing racemic BINAP ligand.

3.5.2 Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian INOVA (500 MHz) spectrometer equipped with a Bruker AVANCE III cryoprobe. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Integration and coupling constants were reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian INOVA (125 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.16 ppm for deuteriochloroform. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian INOVA (470 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00s).

3.5.3 Experimental Details and Spectral Data

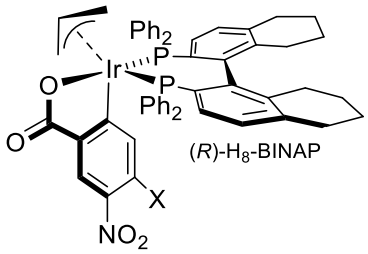
3.5.3.1 Selected Optimization Experiments



Entry	L*	Solvent (M)	Temp (°C)	Yield (%)	ee (%)	dr
1	(*R*)-DTBM-SEGPHOS	THF (0.2 M)	100	<10	N/D	N/D
2	(*R*)-Cl,MeO-BIPHEP	THF (0.2 M)	100	42	87	>20:1
3	(*R*)-Tol-BINAP	THF (0.2 M)	100	31	85	>20:1
4	(*R*)-H_8-BINAP	THF (0.2 M)	100	69	96	>20:1
5	(*R*)-H_8-BINAP	Dioxane (0.2 M)	100	68	94	>20:1
6	(*R*)-H_8-BINAP	PhMe (0.2 M)	100	59	92	>20:1
7	(*R*)-H_8-BINAP	THF (0.5 M)	100	60	94	>20:1
8	(*R*)-H_8-BINAP	THF (0.1 M)	100	37	97	>20:1
9	(*R*)-H_8-BINAP	THF (0.2 M)	90	65	96	>20:1
10	(*R*)-H_8-BINAP	THF (0.2 M)	80	40	96	>20:1
11[a]	(*R*)-H_8-BINAP	THF (0.2 M)	100	71	96	>20:1

[a]150 mol% of phthalimido-allene **3.1** and 48 h reaction time

3.5.3.2 Synthesis of Ir-V and Ir-VI



(*R*)-Ir-V: X = CN
(*R*)-Ir-VI: X = NO_2

To a dried pressure tube with a magnetic stir bar under an argon atmosphere charged with Cs_2CO_3 (586 mg, 1.80 mmol, 225 mol%), the corresponding benzoic acid (1.60 mmol, 200 mol%), (*R*)-H_8-BINAP (505mg, 0.80 mmol, 100 mol%), and $[Ir(cod)Cl]_2$ (268 mg, 0.40 mmol, 50 mol%) was added THF (8 mL, 0.1 M) followed by allyl acetate (0.22 mL, 2.0 mmol, 250 mol%). The resulting mixture was stirred at ambient temperature for 30 min, at which point the reaction vessel was transferred to an oil bath at 80 °C. After stirring for 120 min, the reaction mixture was allowed to cool to ambient temperature. The mixture was filtered through a celite plug with the aid of THF. The filtrate was concentrated in vacuo and the residue subjected to column chromatography (SiO_2, 20:1 DCM:THF). The gum-like product was dissolved in a minimum volume of THF and precipitated upon rapid addition of hexanes. The product was filtered and washed with hexanes, followed by removal of trace amount of solvent in vacuo.

(*R*)-Ir-V: 4-cyano-3-nitrobenzoic acid (307 mg) was used. The title complex was obtained as light yellow powder in 85% yield (716 mg).

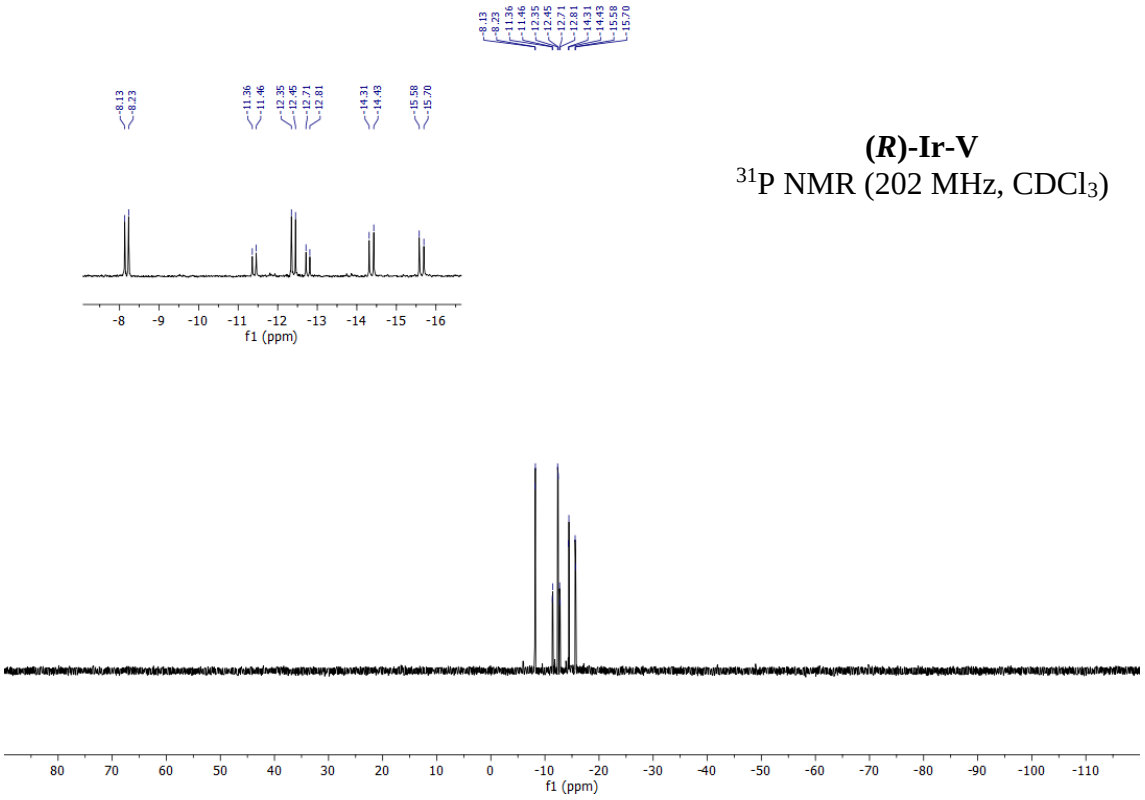
(*R*)-Ir-VI: 3,4-dinitrobenzoic acid (340 mg) was used. The title complex was obtained as light yellow powder in 86% yield (736 mg).

(*R*)-Ir-V:

^{31}P NMR (202 MHz, $CDCl_3$): δ –8.18 (d, *J* = 20.0 Hz), –11.41 (d, *J* = 19.9 Hz), –12.40 (d, *J* = 21.0 Hz), –12.76 (d, *J* = 19.7 Hz), –14.37 (d, *J* = 23.7 Hz), –15.64 (d, *J* = 23.7 Hz).

HRMS (H+, *m/z*) for $C_{55}H_{47}IrN_2O_4P_2$: calcd. = 1053.2690; found = 1053.2675.

MP: [175-182] °C (decomposition)



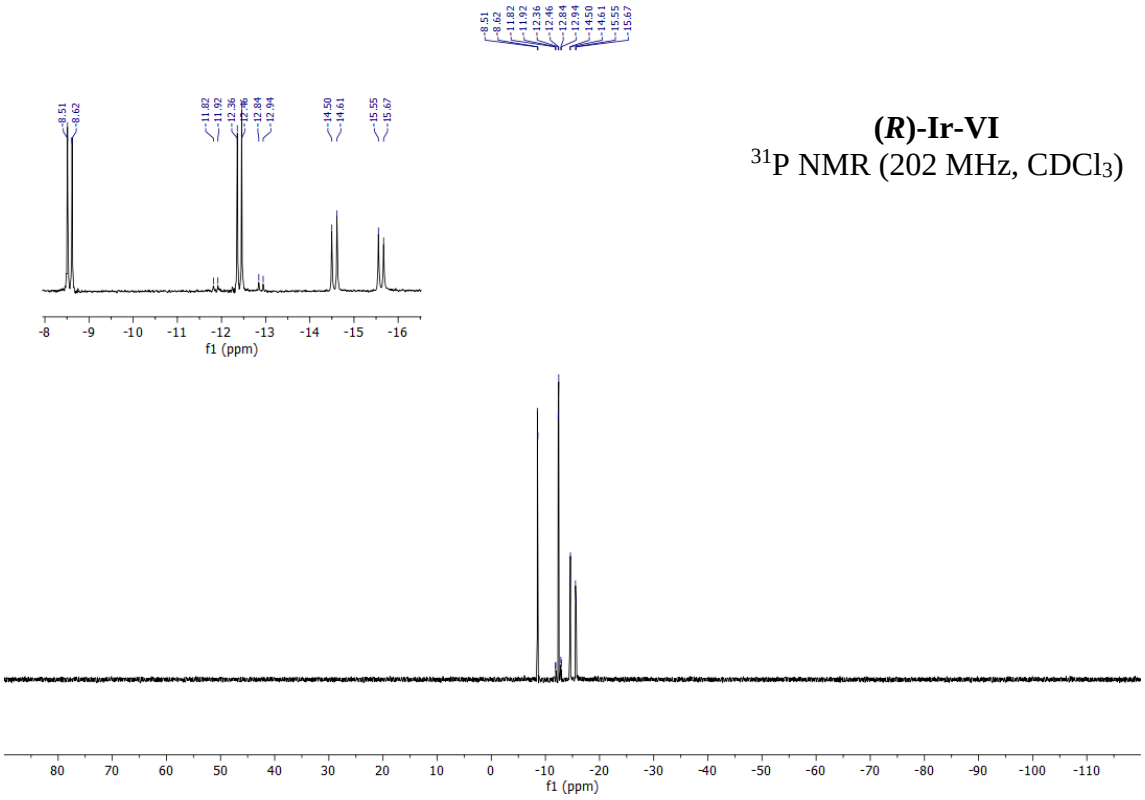
(*R*)-Ir-V
^{31}P NMR (202 MHz, $CDCl_3$)

(*R*)-Ir-VI:

^{31}P NMR (202 MHz, $CDCl_3$): δ -8.56 (d, *J* = 20.7 Hz), -11.87 (d, *J* = 20.1 Hz), -12.41 (d, *J* = 20.0 Hz), -12.89 (d, *J* = 19.9 Hz), -14.56 (d, *J* = 23.7 Hz), -15.61 (d, *J* = 23.7 Hz).

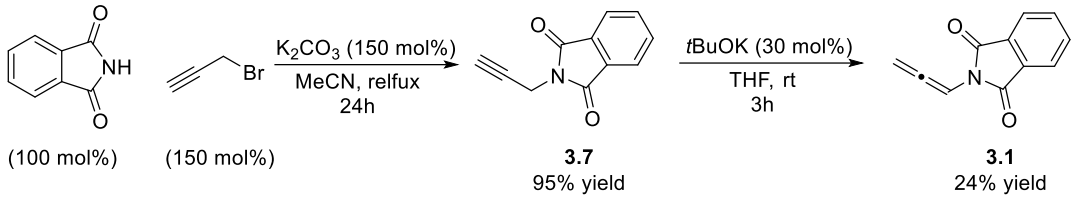
HRMS (H+, *m/z*) for $C_{54}H_{47}IrN_2O_6P_2$: calcd. = 1073.2588; found = 1073.2579.

MP: [226-232] °C (decomposition)

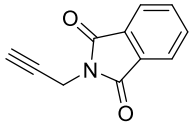


(*R*)-Ir-VI
^{31}P NMR (202 MHz, $CDCl_3$)

3.5.3.3 Synthesis of Phthalimido-Allene 3.1



Synthesis of N-Propargylphthalimide (3.7)



3.7

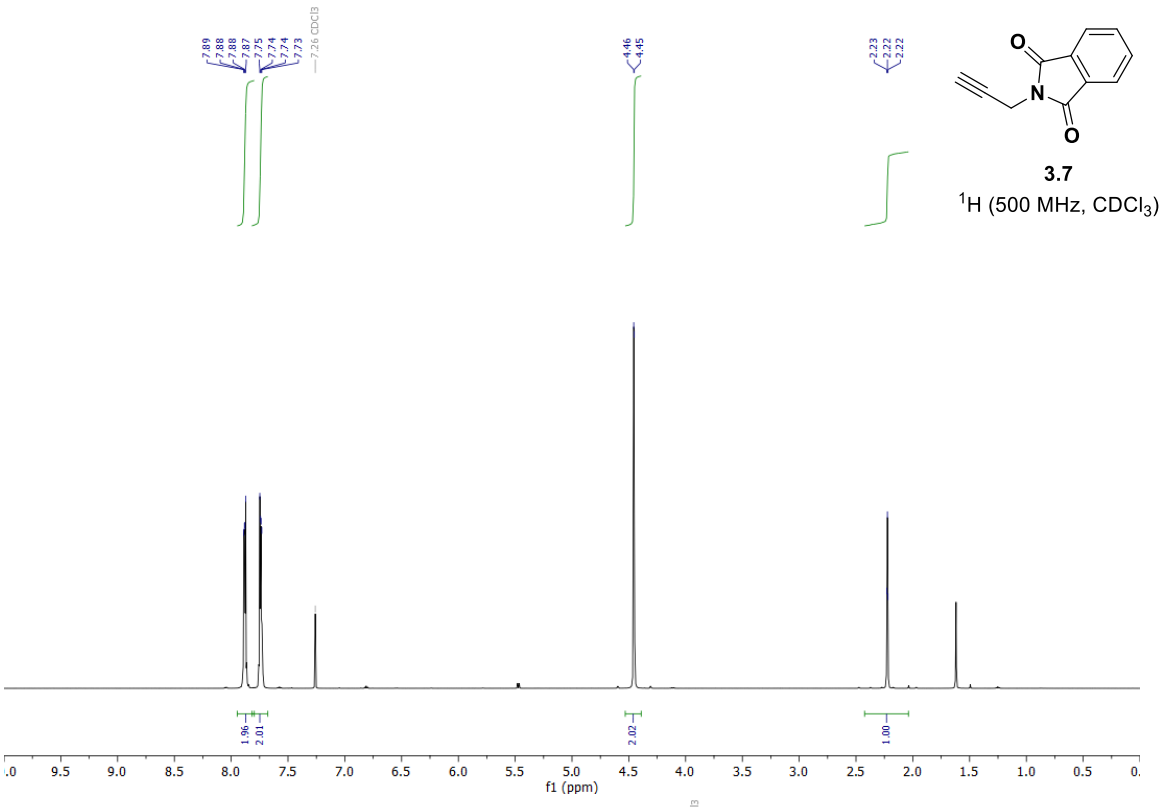
3.7 can also be purchased and used from Combi-Blocks.

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with phthalimide (15.2 g, 103 mmol, 100 mol%) and K_2CO_3 (21.4 g, 155 mmol, 150 mol%) in CH_3CN (250 mL) was added propargyl bromide (80% wt in PhMe, 23.0 g, 155 mmol, 150 mol%). The reaction mixture was allowed to stir for 24 hours at reflux. The hot reaction mixture was then filtered through a pad of Celite and washed with CH_3CN (3 x 15 mL). The mixture was then concentrated under reduced pressure. The residue was then solubilized in DCM, resulting in a suspension of starting material which was then filtered off through a pad of Celite. The resulting residue was concentrated under reduced pressure, dissolved in a minimum volume of DCM, and precipitated upon rapid addition of pentane. The product was filtered and washed with pentane, followed by removal of trace amount of solvent in vacuo, to provide a white solid (18.1 g, 97.8 mmol) in 95% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.45 (d, *J* = 2.5 Hz, 1H), 2.22 (t, *J* = 2.5 Hz, 1H).

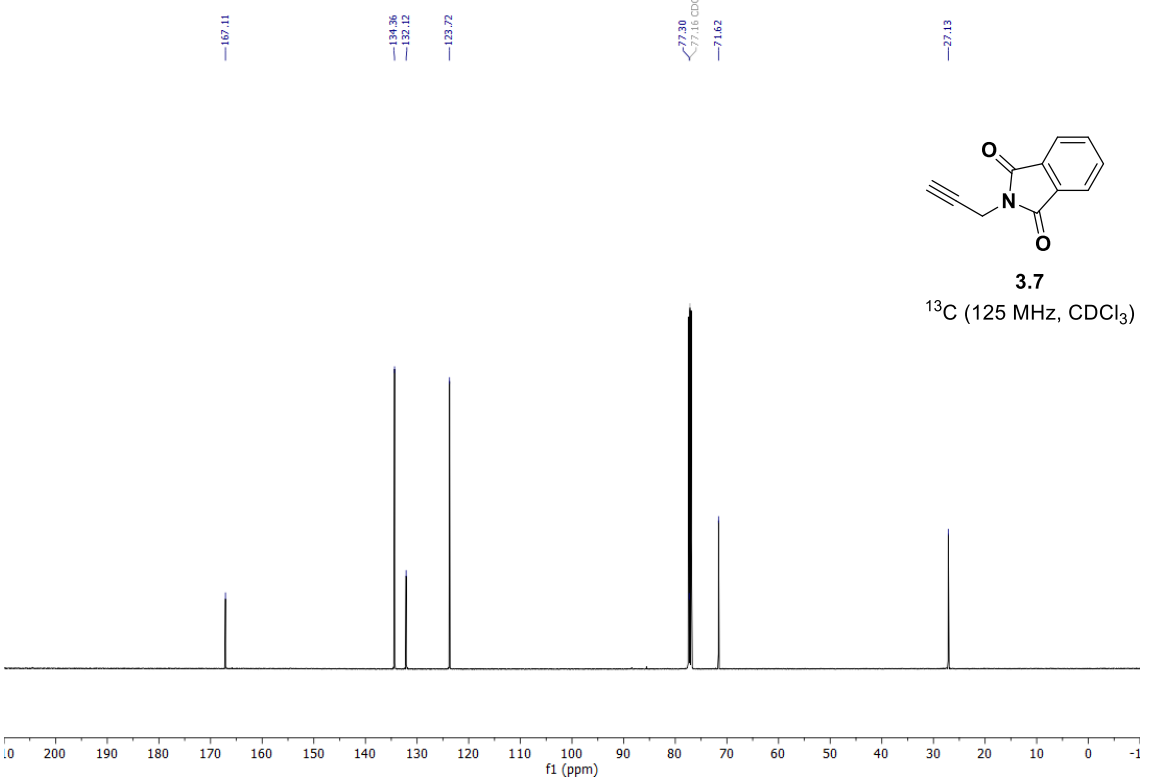
^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.1, 134.4, 132.1, 123.7, 77.3, 71.6, 27.1.

The spectral data recorded for the compound was in complete agreement with the literature.[24]



3.7

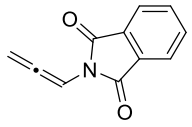
^{1}H (500 MHz, $CDCl_3$)



3.7

^{13}C (125 MHz, $CDCl_3$)

Phthalimido-Allene (3.1)



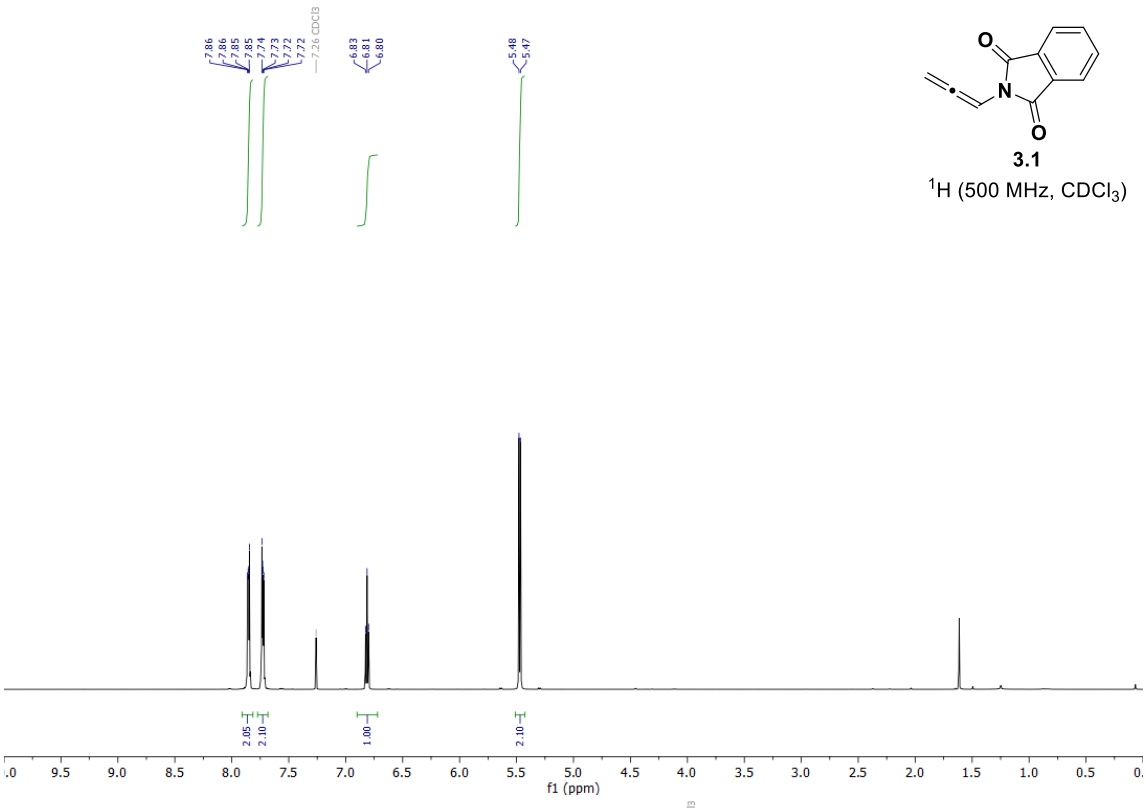
3.1

To a round-bottomed flask equipped with a magnetic stir bar under an argon atmosphere charged with N-propargylphthalimide **3.7** (9.26 g, 50.0 mmol, 100 mol%) in dried THF (50 mL) was added potassium *tert*-butoxide (1.68 g, 15 mmol, 30 mol%). The reaction mixture was allowed to stir at ambient temperature for 3 hours. The reaction mixture was then filtered through a pad of Celite, washed with THF, and the solvent removed in vacuo. The residue was purified by flash column chromatography (SiO_2, 0-10% EtOAc in hexanes) to give the phthalimido-allene (2.21 g, 11.9 mmol) as a pale green crystalline solid in 24% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.81 (t, *J* = 6.7 Hz, 1H), 5.47 (d, *J* = 6.6 Hz, 1H).

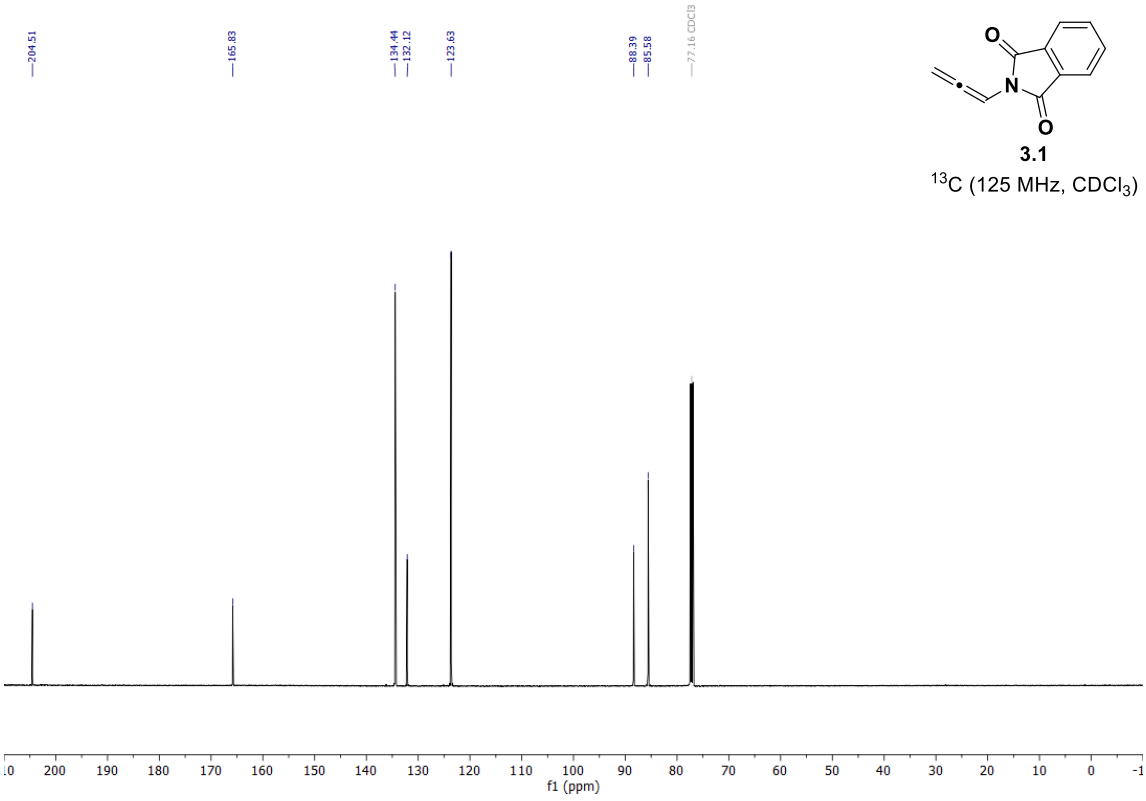
^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.5, 165.8, 134.4, 133.1, 123.6, 88.4, 85.6.

The spectral data recorded for the compound was in complete agreement with the literature.[11b]



3.1

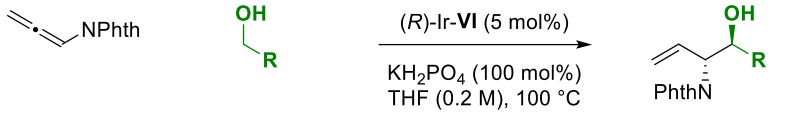
^{1}H (500 MHz, $CDCl_3$)



3.1

^{13}C (125 MHz, $CDCl_3$)

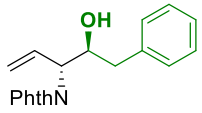
3.5.3.4 General Procedure and Spectral Data for the Coupling of Phthalimido-Allene and Alcohols



3.1 (150 mol%) **3.2[a–z, a'–c']** (100 mol%) **3.3[a–z, a'–c']**

To a dried pressure tube with a magnetic stir bar under an argon atmosphere charged with (*R*)-Ir-**VI** (10.7 mg, 0.01 mmol) (5 mol%), phthalimido-allene **3.1** (55 mg, 0.3 mmol, 150 mol%), alcohol (0.2 mmol, 100 mol%), and KH_2PO_4 (27.2 mg, 0.2 mmol, 100 mol%) was added THF (1.0 mL, 0.2 M). The tube was sealed with a PTFE lined cap and the reaction mixture was allowed to stir for 48 hours at 100 °C. After reaching ambient temperature, the solvent was removed in vacuo and the residue was subjected to flash column chromatography (SiO_2) under the noted conditions to furnish the products **3.3[a–z, a'–c']**.

2-((3*R*,4*S*)-4-hydroxy-5-phenylpent-1-en-3-yl)isoindoline-1,3-dione (3.3a)



3.3a

Alcohol **3.2a** (24.0 µL, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3a** (48.8 mg, 0.16 mmol, >20:1 dr) was obtained as a light yellow solid in 80% yield.

TLC (SiO_2) R_f = 0.35 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.28 – 7.15 (m, 5H), 6.34 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.36 (d, *J* = 10.7 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 4.78 – 4.76 (m, 1H), 4.41 (ddd, *J* = 7.7, 5.8, 4.7 Hz, 1H), 3.45 (brs, 1H), 2.90 – 2.81 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 137.9, 134.4, 131.8, 131.4, 129.4, 128.7, 126.7, 123.7, 120.4, 73.0, 58.7, 40.9.

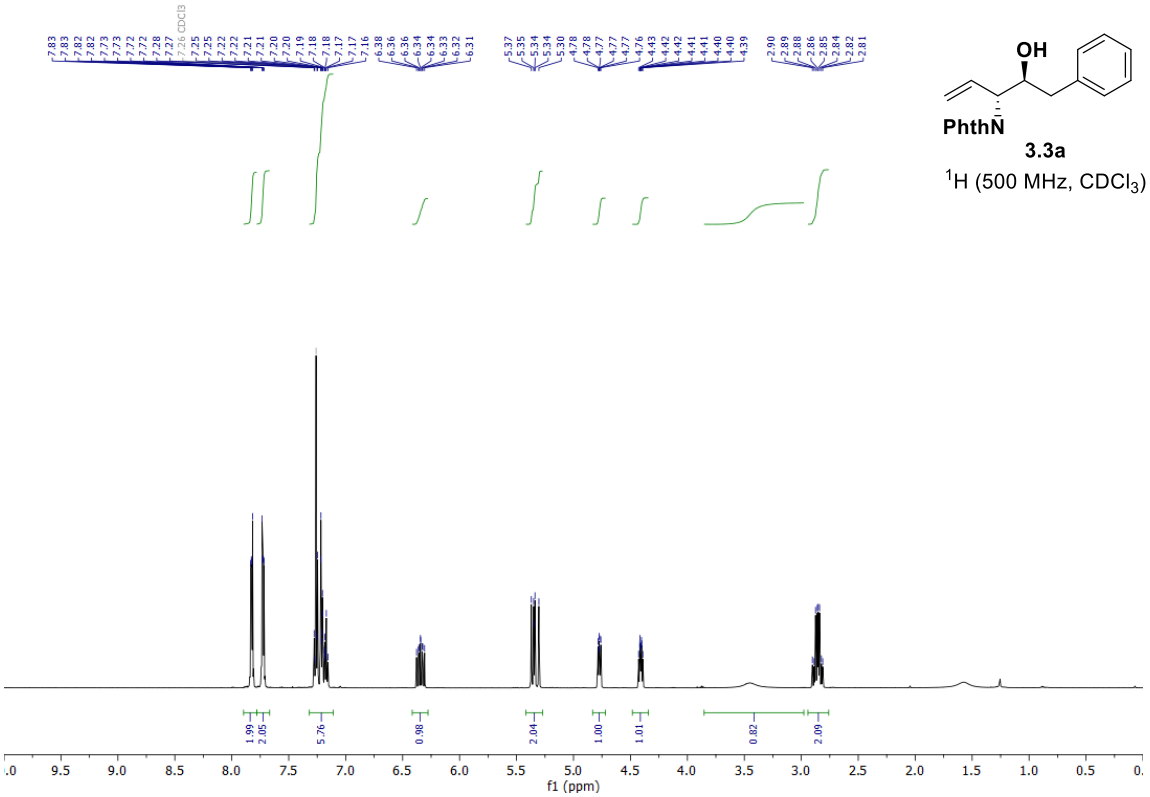
HRMS (Na+, *m/z*) for $C_{19}H_{17}NO_3$: calcd. = 330.1101; found = 330.1104.

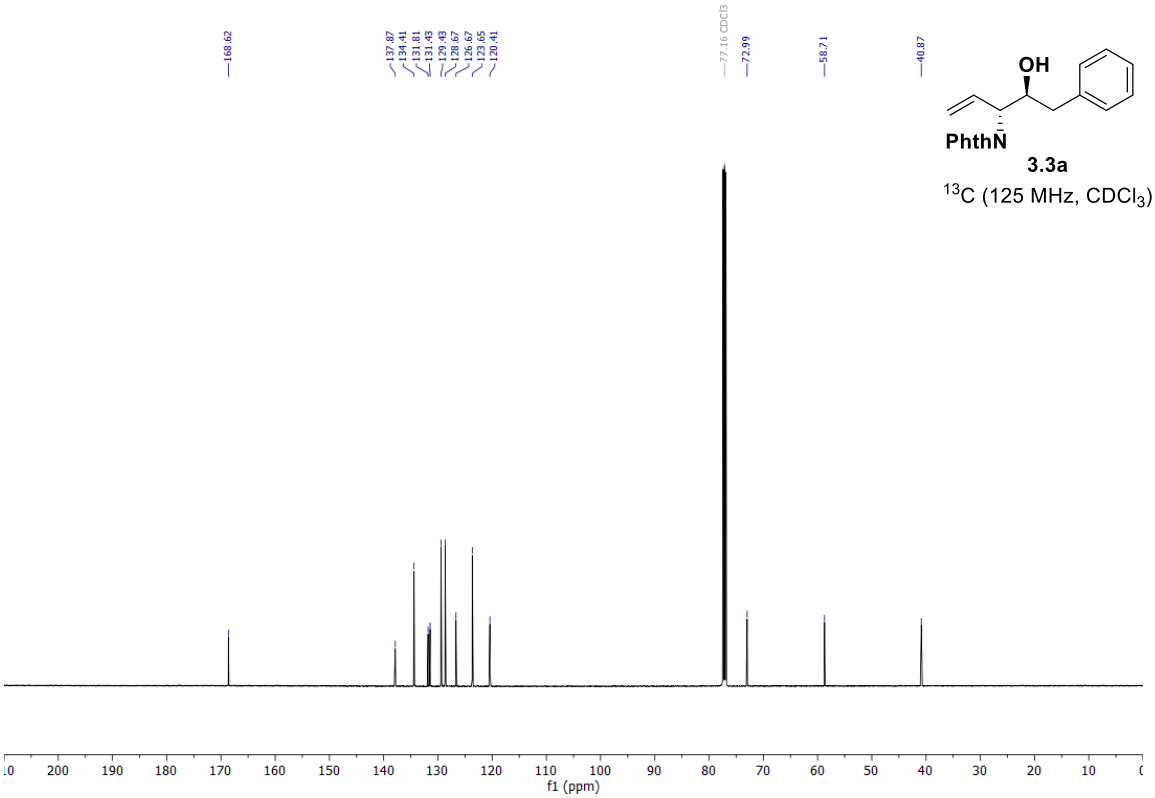
FTIR (neat): 3549, 1698, 1383, 1334, 1055, 721, 703.

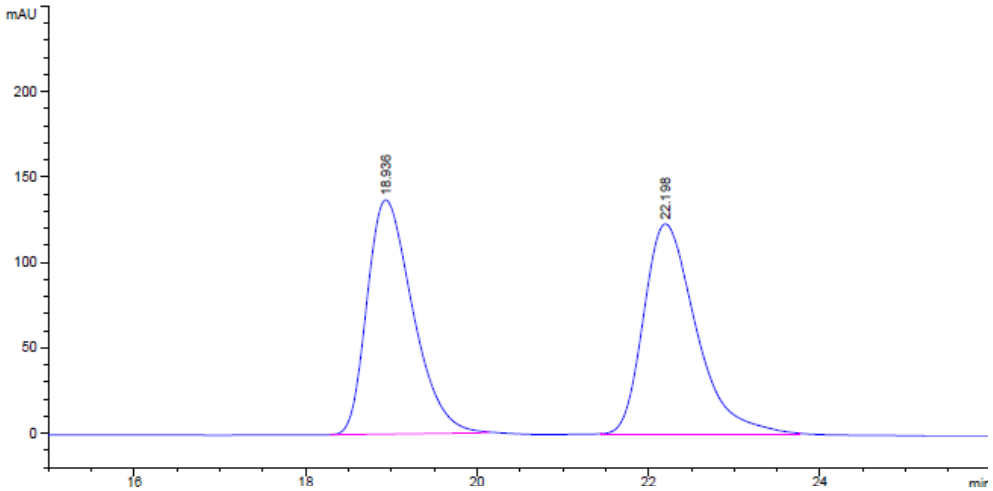
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +56.6° (c = 1.31, $CHCl_3$).

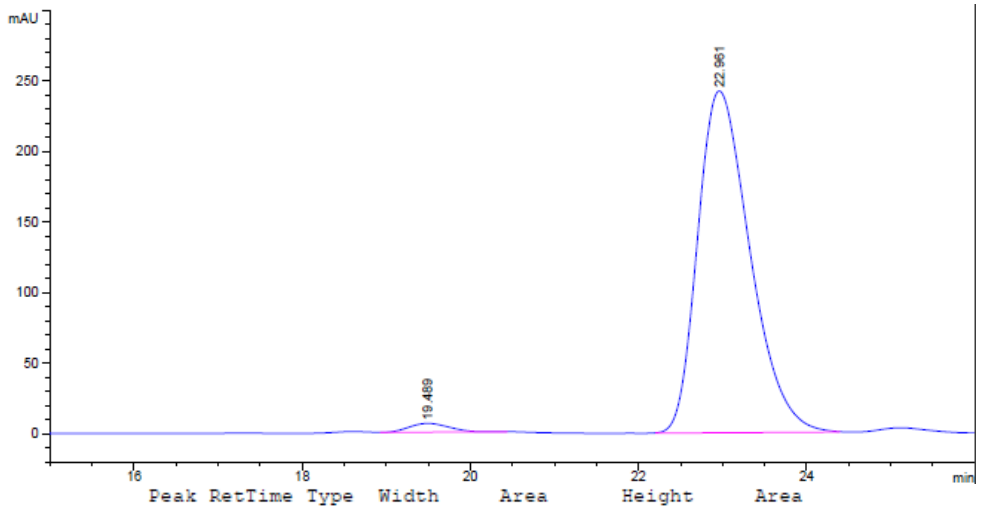
MP [121 – 126] °C


OH
PhthN
3.3a
1H (500 MHz, CDCl3)
f1 (ppm)


OH
PhthN
3.3a
13C (125 MHz, CDCl3)
f1 (ppm)

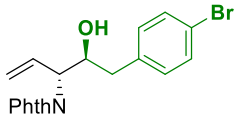


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.936	BB	0.5717	5072.34863	137.07306	49.2480
2	22.198	BB	0.6519	5227.26367	122.98929	50.7520



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.489	BB	0.4877	207.63521	6.21617	1.9457
2	22.961	BB	0.6719	1.04640e4	242.27353	98.0543

2-((3*R*,4*S*)-5-(4-bromophenyl)-4-hydroxypent-1-en-3-yl)isoindoline-1,3-dione (3.3b)



3.3b

Alcohol **3.2b** (40.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3b** (49.9 mg, 0.13 mmol, >20:1 dr) was obtained as a pale yellow oil in 65% yield.

TLC (SiO_2) R_f = 0.33 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.32 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.36 (d, *J* = 10.7 Hz, 1H), 5.33 (d, *J* = 17.0 Hz, 1H), 4.75 – 4.72 (m, 1H), 4.39 – 4.35 (m, 1H), 3.47 (brs, 1H), 2.86 – 2.75 (m, 2H).

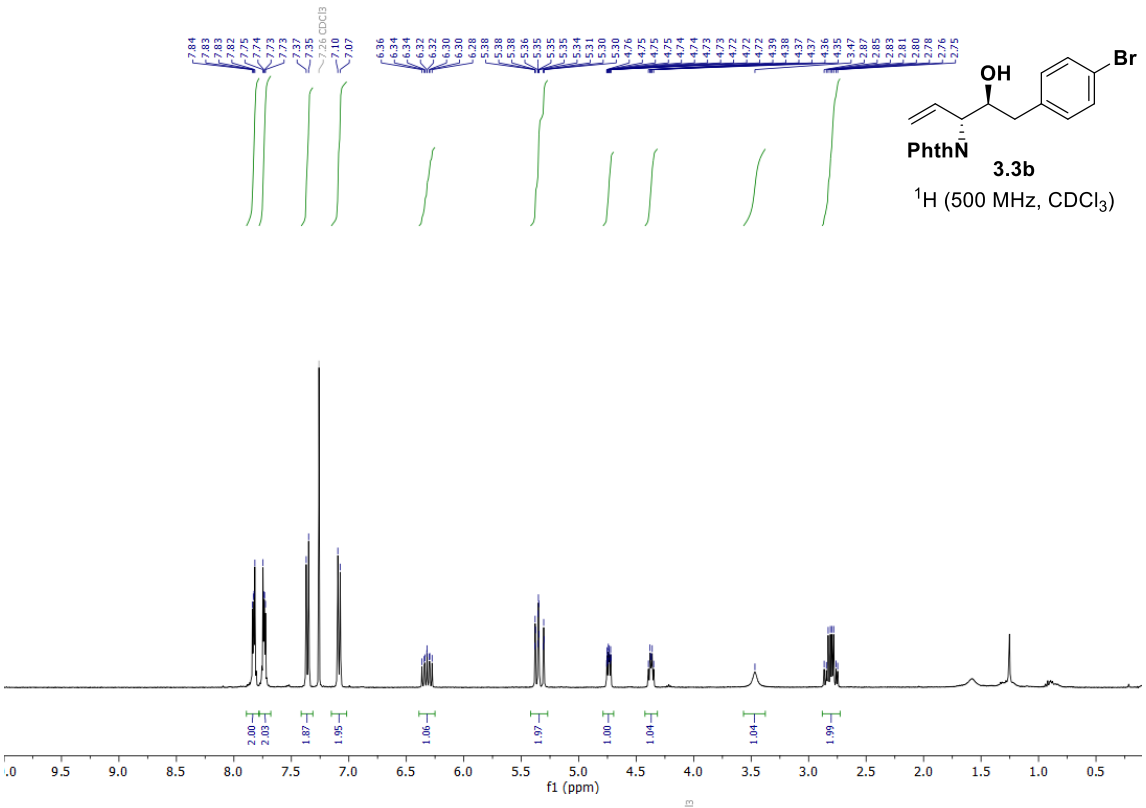
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 137.0, 134.5, 131.7, 131.7, 131.3, 131.4, 123.7, 120.7, 120.6, 72.6, 58.9, 40.3.

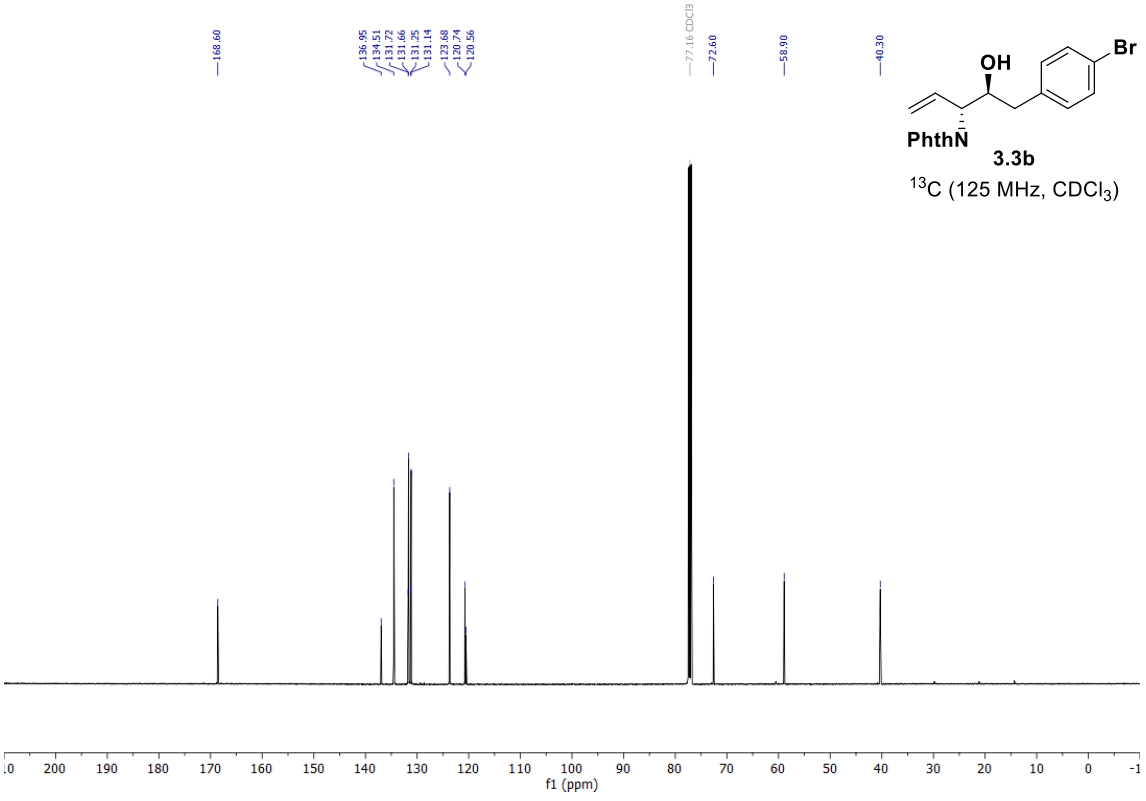
HRMS (H+, *m/z*) for $C_{19}H_{16}BrNO_3$: calcd. = 386.0386; found = 386.0380.

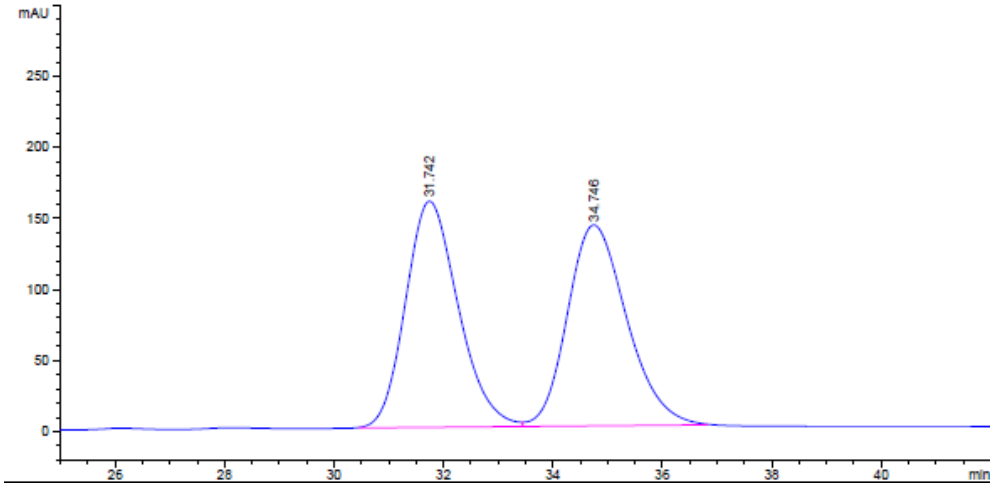
FTIR (neat): 3454, 2919, 2359, 1700, 1380, 1070, 717.

HPLC: (Chiralcel column AS-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 97%.

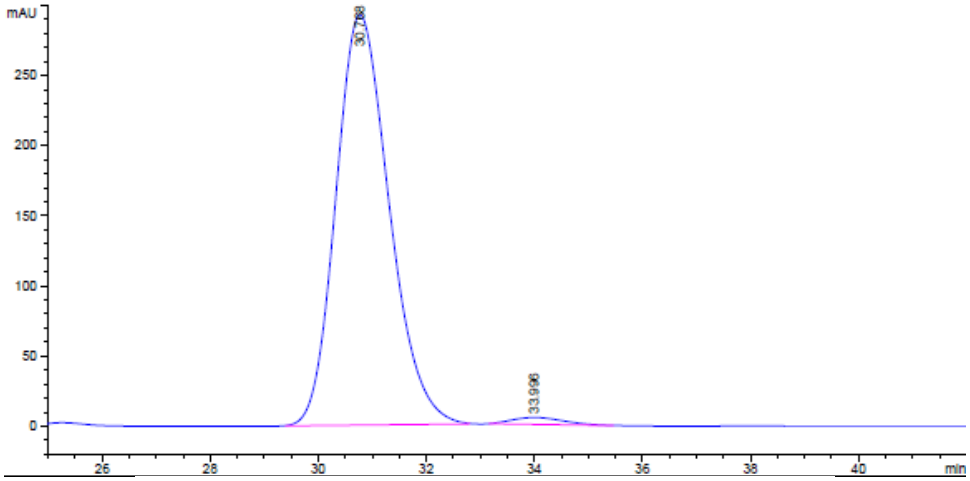
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +47.9° (c = 0.93, $CHCl_3$).


OH
Br
PhthN
3.3b
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


OH
Br
PhthN
3.3b
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

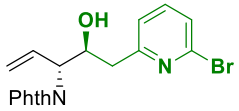


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.742	BV	1.0092	1.06599e4	159.19156	49.9904
2	34.746	VB	1.1439	1.06640e4	141.39439	50.0096



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.768	BB	1.0595	2.00459e4	292.51804	98.3845
2	33.996	BB	0.7972	329.15945	4.96634	1.6155

2-((3*R*,4*S*,*E*)-4-hydroxy-6-phenylhexa-1,5-dien-3-yl)isoindoline-1,3-dione (3.3c)



3.3c

Alcohol **3.2c** (40.4 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3c** (47.1 mg, 0.12 mmol, >20:1 dr) was obtained as a light yellow oil in 61% yield.

TLC (SiO_2) R_f = 0.31 (40:60 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.39 (ddd, *J* = 17.7, 10.3, 7.7 Hz, 1H), 5.35 – 5.30 (m, 2H), 4.79 (dd, *J* = 7.9, 5.3 Hz, 1H), 4.64 (dt, *J* = 8.1, 4.8 Hz, 1H), 3.01 – 2.93 (m, 2H).

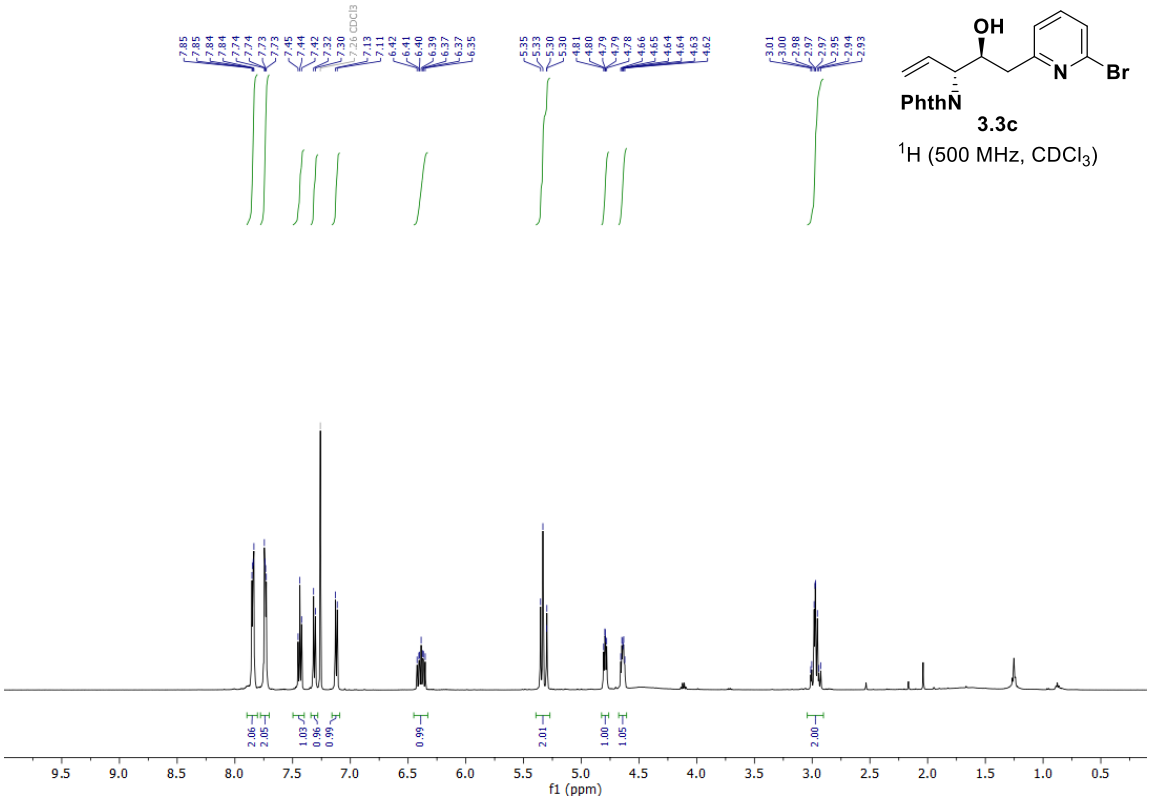
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 160.3, 141.4, 138.9, 134.4, 131.8, 131.7, 126.2, 123.7, 123.1, 120.2, 71.3, 58.8, 41.4.

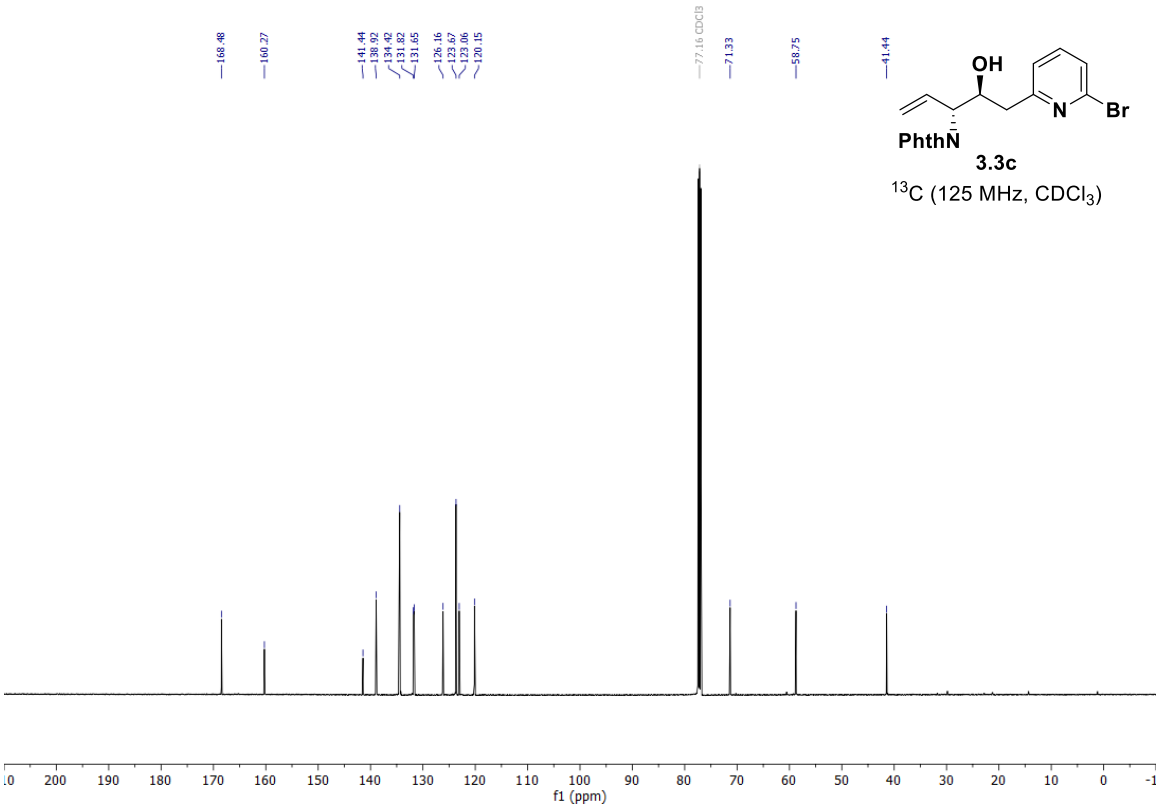
HRMS (H+, *m/z*) for $C_{18}H_{15}BrN_2O_3$: calcd. = 387.0339; found = 387.0334.

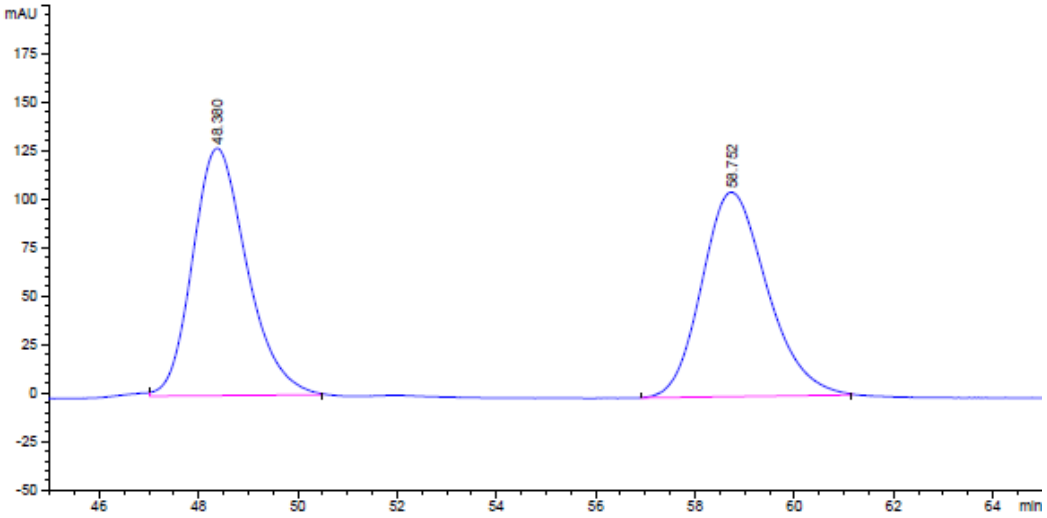
FTIR (neat): 3446, 1704, 1380, 1064, 751, 718.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 96%.

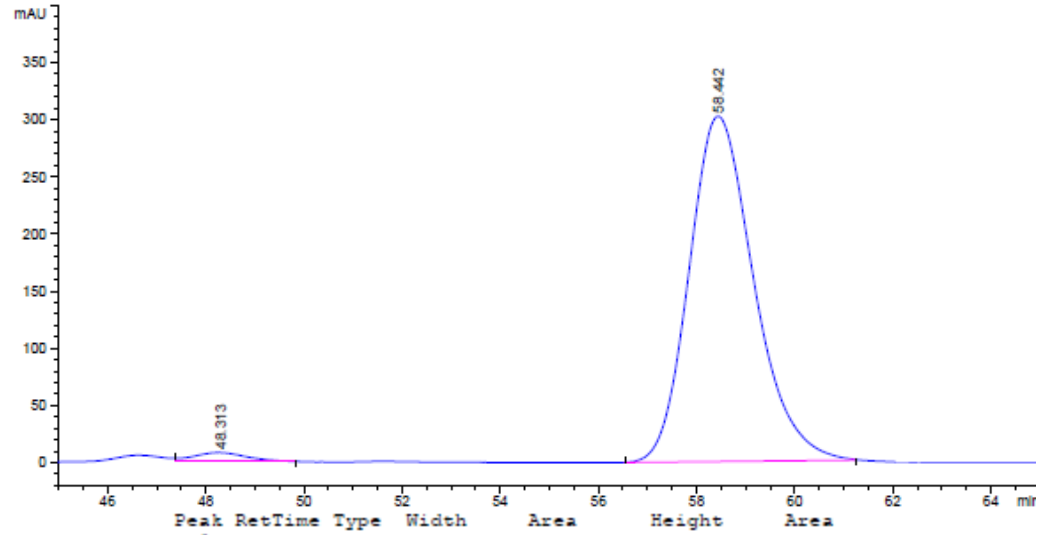
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$ = +47.5° (c = 0.80, $CHCl_3$).


OH
N
Br
PhthN
3.3c
1H (500 MHz, CDCl3)
f1 (ppm)


OH
N
Br
PhthN
3.3c
13C (125 MHz, CDCl3)
f1 (ppm)

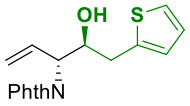


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.380	BB	1.0714	9698.82227	127.51176	50.1195
2	58.752	BB	1.0808	9652.58301	105.36746	49.8805



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.313	VB	0.8977	592.82471	7.80895	2.0989
2	58.442	BB	1.1362	2.76517e4	302.00626	97.9011

2-((3*R*,4*S*)-4-hydroxy-5-(thiophen-2-yl)pent-1-en-3-yl)isoindoline-1,3-dione (3.3d)



3.3d

Alcohol **3.2d** (25.6 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3d** (42.0 mg, 0.13 mmol, >20:1 dr) was obtained as a white solid in 67% yield.

TLC (SiO_2) R_f = 0.28 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.94 – 6.91 (m, 1H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.37 – 6.27 (m, 1H), 5.34 (dd, *J* = 19.6, 13.7 Hz, 2H), 4.80 (dd, *J* = 7.8, 4.3 Hz, 1H), 4.43 – 4.32 (m, 1H), 3.76 (s, 1H), 3.08 (d, *J* = 6.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 139.8, 134.5, 131.8, 131.0, 127.0, 126.3, 124.5, 123.7, 120.6, 77.2, 73.1, 58.4, 34.9.

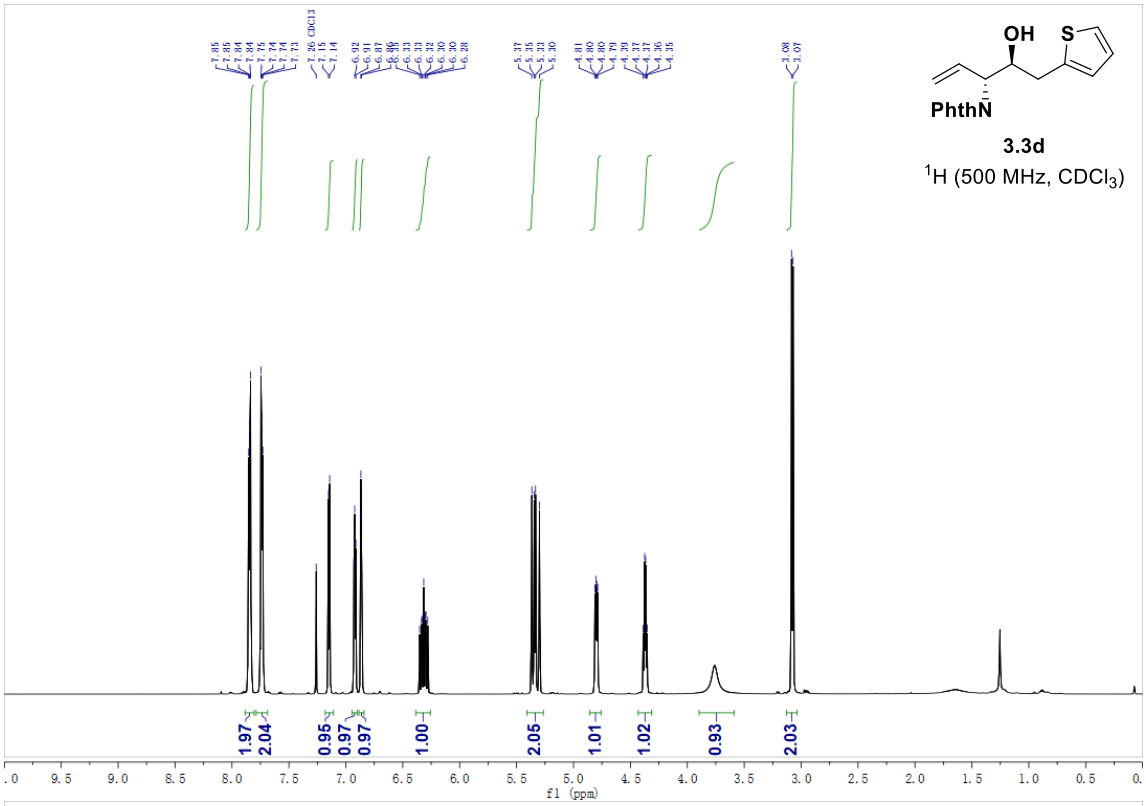
HRMS (Na+, *m/z*) for $C_{17}H_{15}NO_3S$: calcd. = 336.0665; found = 336.0667.

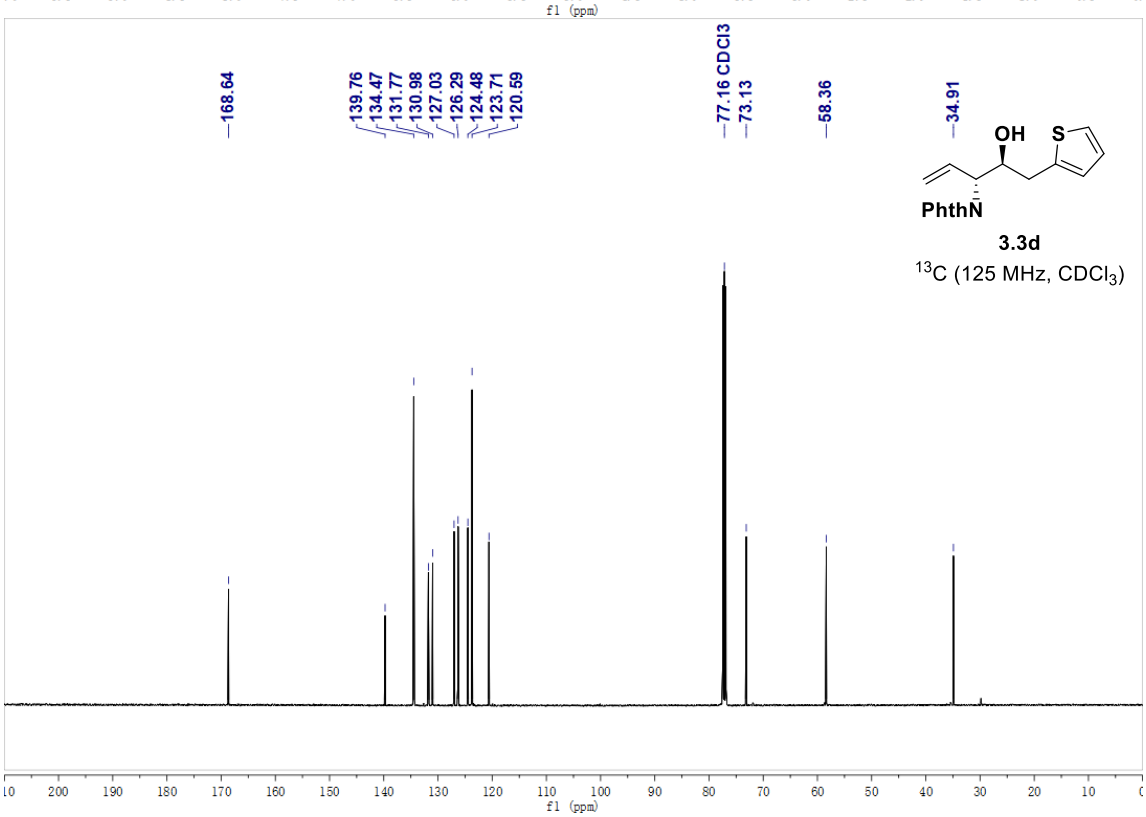
FTIR (neat): 3451, 2360, 2341, 1703, 1381, 1261, 1063, 749.

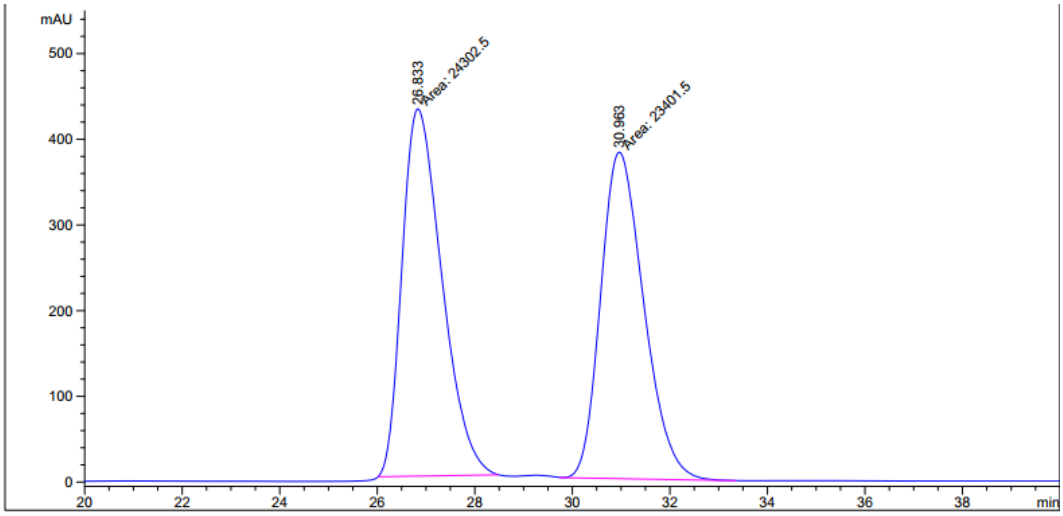
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 92%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +72.3° (c = 0.4, $CHCl_3$).

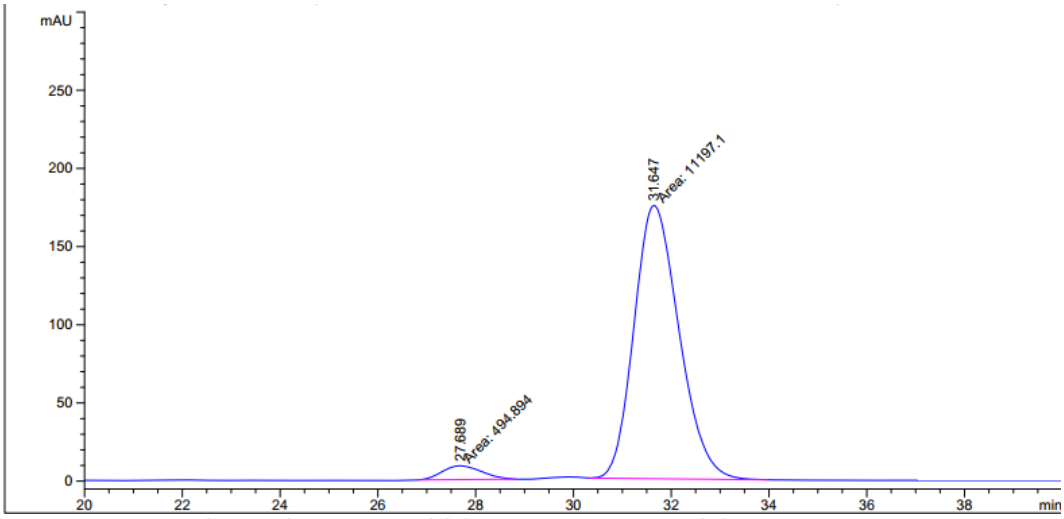
MP: [80 – 84] °C


OH
S
PhthN
3.3d
1H (500 MHz, CDCl3)
1.97
2.04
0.95
0.97
0.97
1.00
2.05
1.01
1.02
0.93
2.03
f1 (ppm)


168.64
139.76
134.47
131.77
130.98
127.03
126.29
124.48
123.71
120.59
77.16 CDCl3
73.13
68.36
34.91
OH
S
PhthN
3.3d
13C (125 MHz, CDCl3)
f1 (ppm)

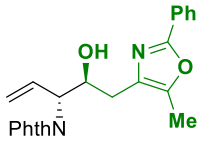


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.833	MM	0.9451	2.43025e4	428.55585	50.9444
2	30.963	MM	1.0235	2.34015e4	381.08691	49.0556



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.689	MM	0.9312	494.89352	8.85730	4.2327
2	31.647	MM	1.0678	1.11971e4	174.77449	95.7673

2-((3*R*,4*S*)-4-hydroxy-5-(5-methyl-2-phenyloxazol-4-yl)pent-1-en-3-yl)isoindoline-1,3-dione (3.3e)



3.3e

Alcohol **3.2e** (40.6 mg, 0.2 mmol) was subjected to standard reaction conditions with 7.5 mol% catalyst (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3e** (54.9 mg, 0.14 mmol, >20:1 dr) was obtained as a white solid in 71% yield.

TLC (SiO_2) R_f = 0.4 (40:60 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.91 (m, 2H), 7.82-7.81 (m, 2H), 7.70-7.69 (m, 2H), 7.42-7.39 (m, 3H), 6.41 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 5.32 (ddt, *J* = 7.4, 3.0, 1.2 Hz, 2H), 4.79 (ddt, *J* = 7.5, 6.2, 1.1 Hz, 1H), 4.61 (td, *J* = 6.7, 4.9 Hz, 1H), 2.70 (ddd, *J* = 4.8, 15.0, 37.7 Hz, 2H), 2.23 (s, 3H), 1.64 (bs, 1H).

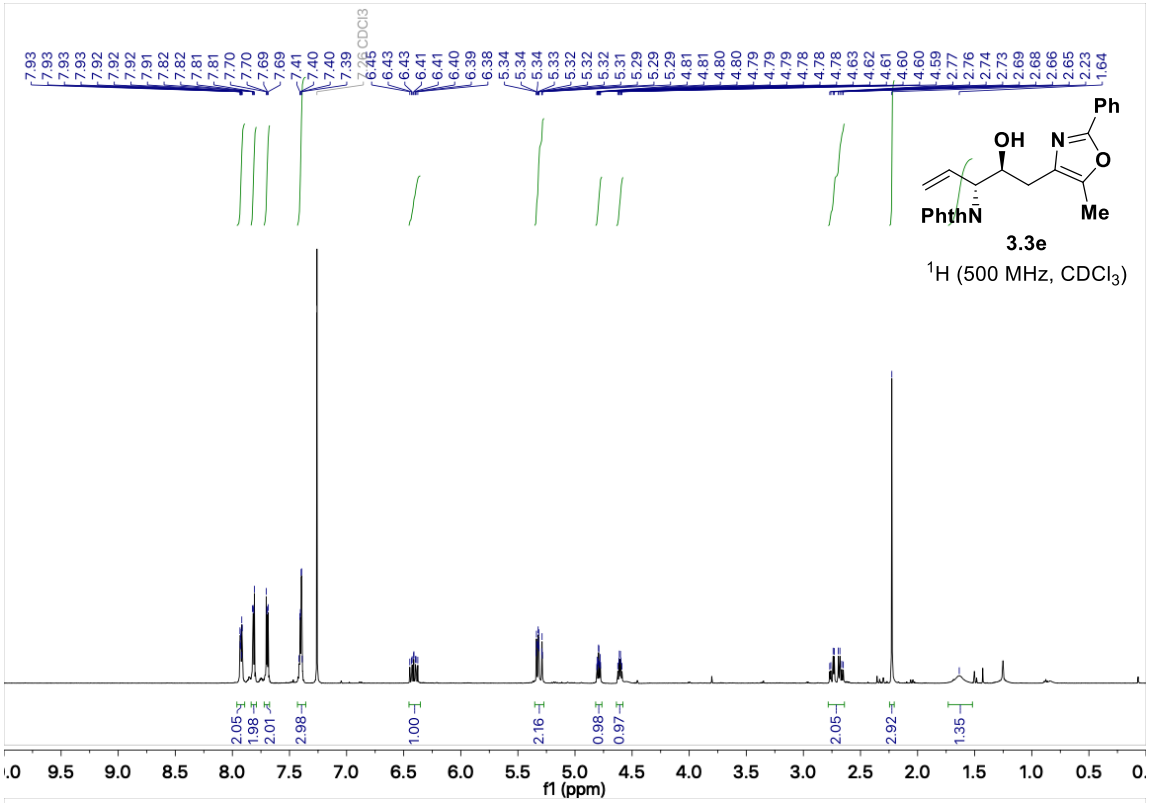
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.6, 145.0, 134.3, 132.5, 132.3, 131.8, 130.2, 128.8, 127.4, 126.2, 123.5, 119.7, 70.9, 58.3, 29.8, 10.3.

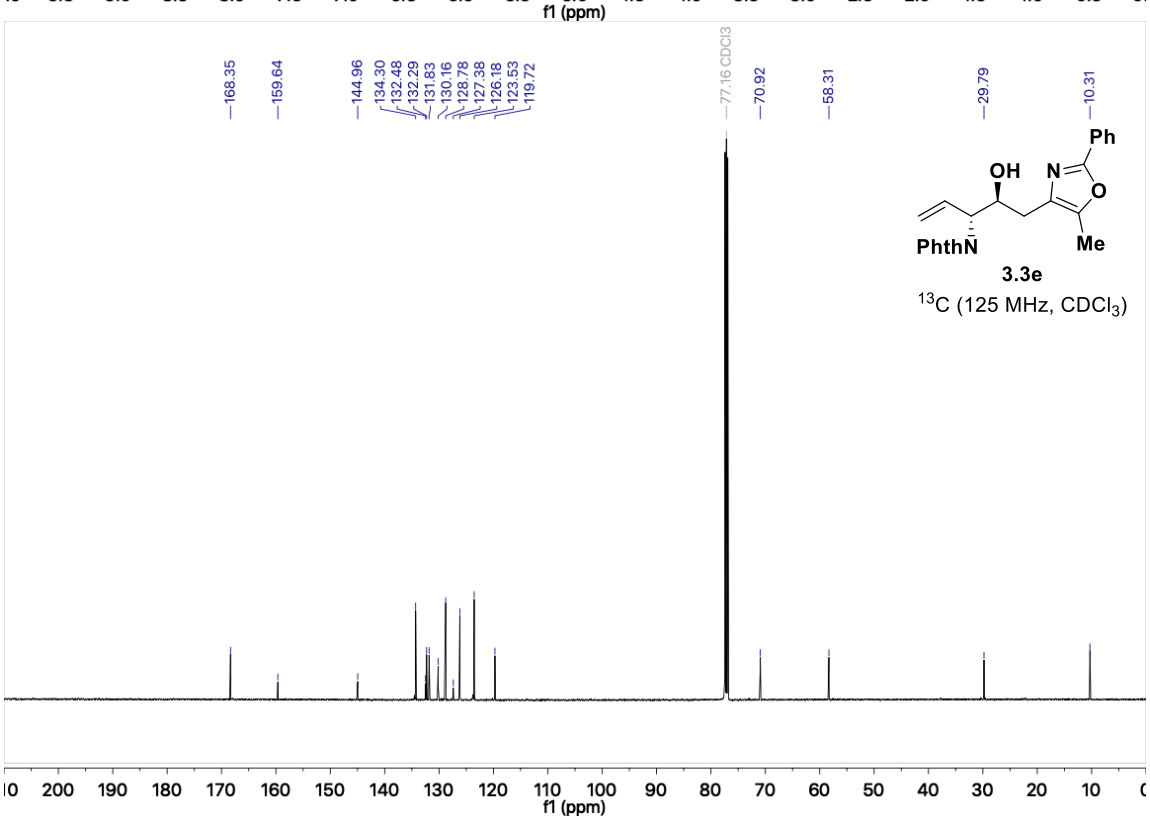
HRMS (H+, *m/z*) for $C_{23}H_{21}N_2O_4$: calcd. = 389.1496; found = 389.1499.

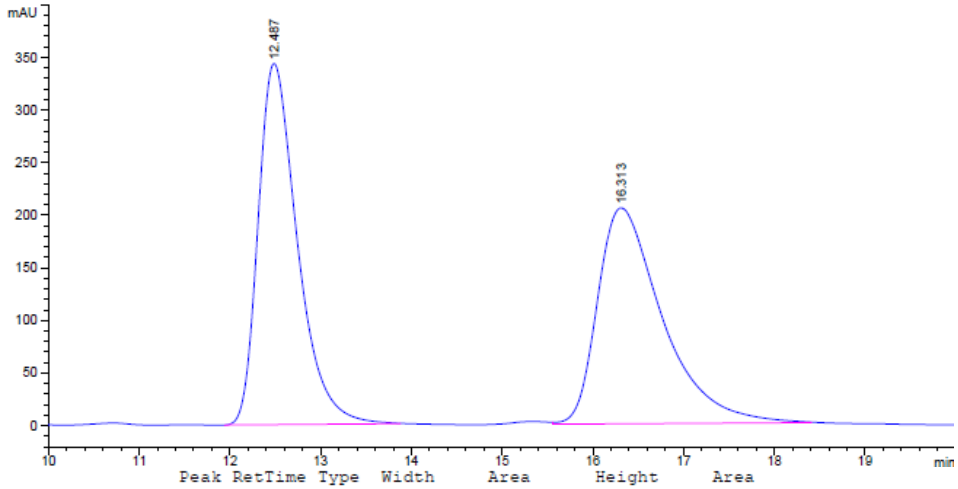
FTIR (neat): 2923, 2853, 1710, 1382, 1334, 1066, 718, 692.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 90:10, 1.0 mL/min, 230 nm) ee = 96%.

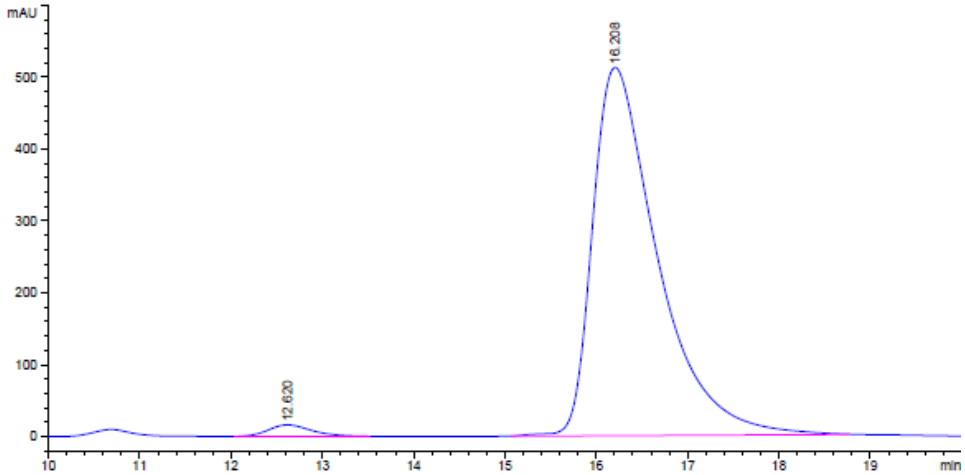
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +23.8° (c = 1.3, $CHCl_3$).


Ph
OH
N
O
PhthN
Me
3.3e
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


Ph
OH
N
O
PhthN
Me
3.3e
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

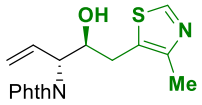


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.487	BB	0.4589	1.03227e4	343.20798	50.2761
2	16.313	VB	0.7523	1.02094e4	205.26210	49.7239



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.620	BB	0.5049	534.04919	16.10544	2.0688
2	16.208	BB	0.7320	2.52809e4	512.01331	97.9312

2-((3*R*,4*S*)-4-hydroxy-5-(4-methylthiazol-5-yl)pent-1-en-3-yl)isoindoline-1,3-dione (3.3f)



3.3f

Alcohol **3.2f** (28.6 mg, 0.2 mmol) was subjected to standard reaction conditions with longer reaction time (100 °C, 72 h). Upon flash column chromatography (SiO_2, 50:50 EtOAc:hexanes), the title compound **3.3f** (47.0 mg, 0.144 mmol, >20:1 dr) was obtained as a white solid in 72% yield.

TLC (SiO_2) R_f = 0.29 (60:40 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.37 – 6.24 (m, 1H), 5.41 – 5.23 (m, 2H), 4.75 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.31 (dt, *J* = 7.9, 5.0 Hz, 1H), 4.09 (d, *J* = 6.8 Hz, 1H), 3.03 – 2.92 (m, 2H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 150.4, 150.0, 134.6, 131.7, 130.9, 127.0, 123.7, 120.8, 72.6, 58.7, 31.4, 15.2.

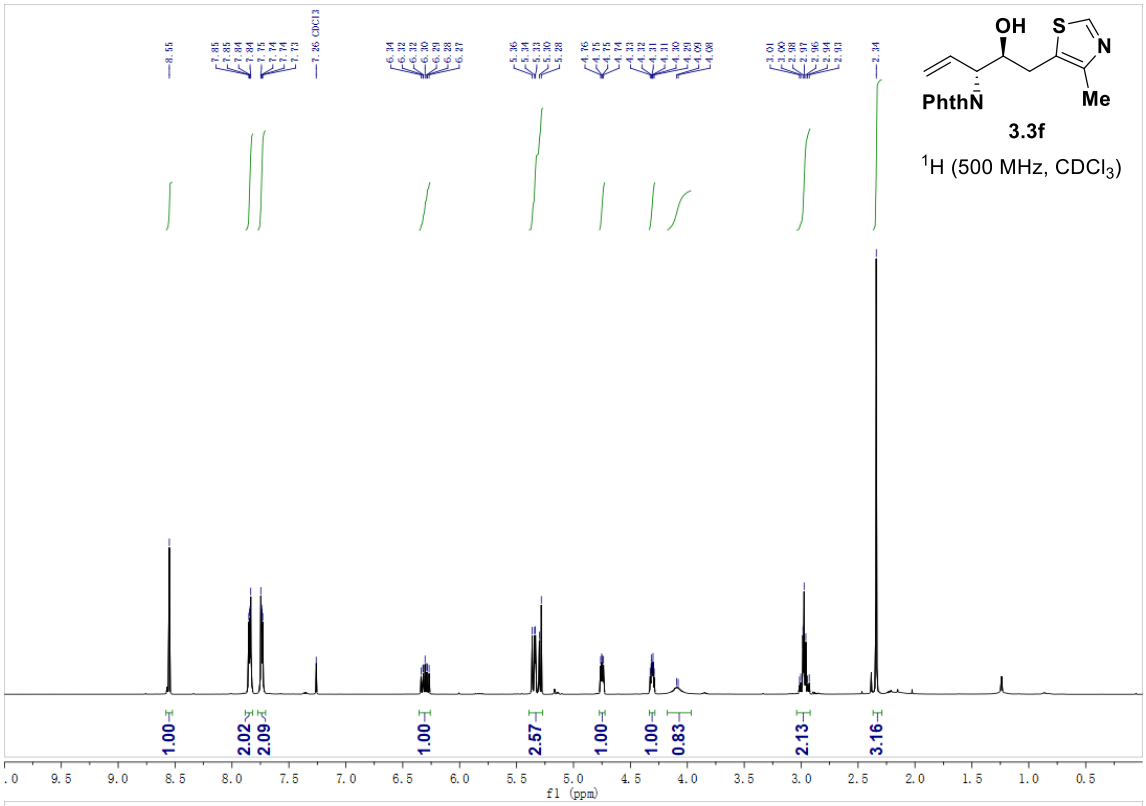
HRMS (H+, *m/z*) for $C_{17}H_{17}N_2O_3S$: calcd. = 329.0954; found = 329.0957.

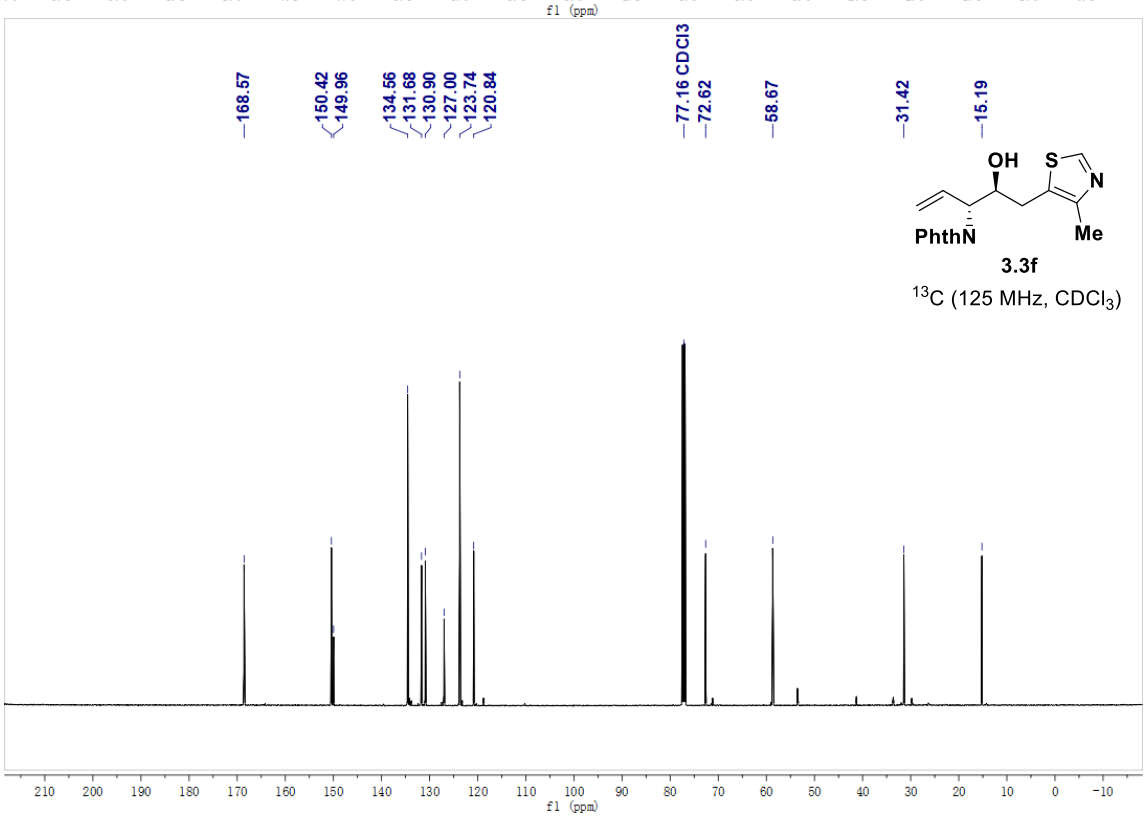
FTIR (neat): 3724, 3004, 2360, 2341, 1706, 1275, 260, 750, 669.

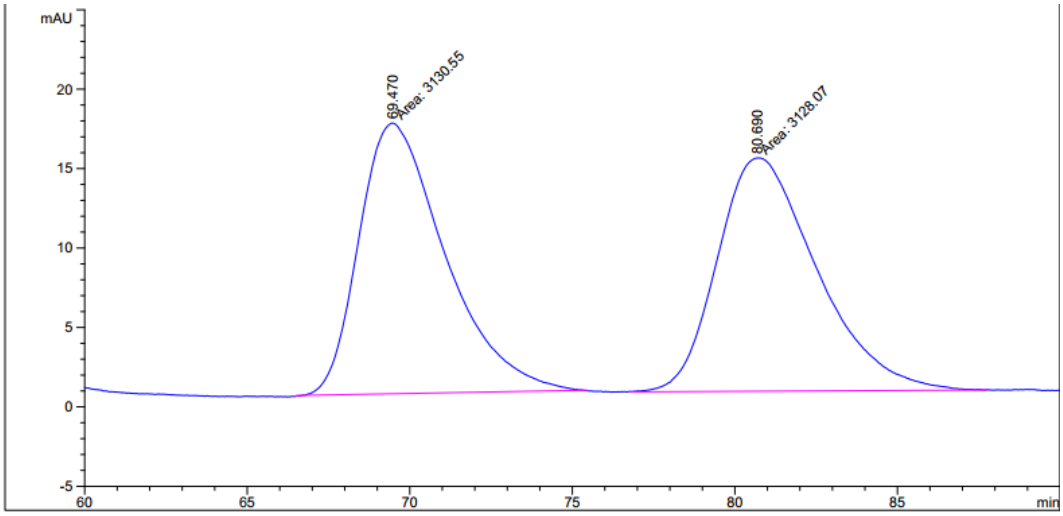
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 94%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +15.7° (c = 0.87, $CHCl_3$).

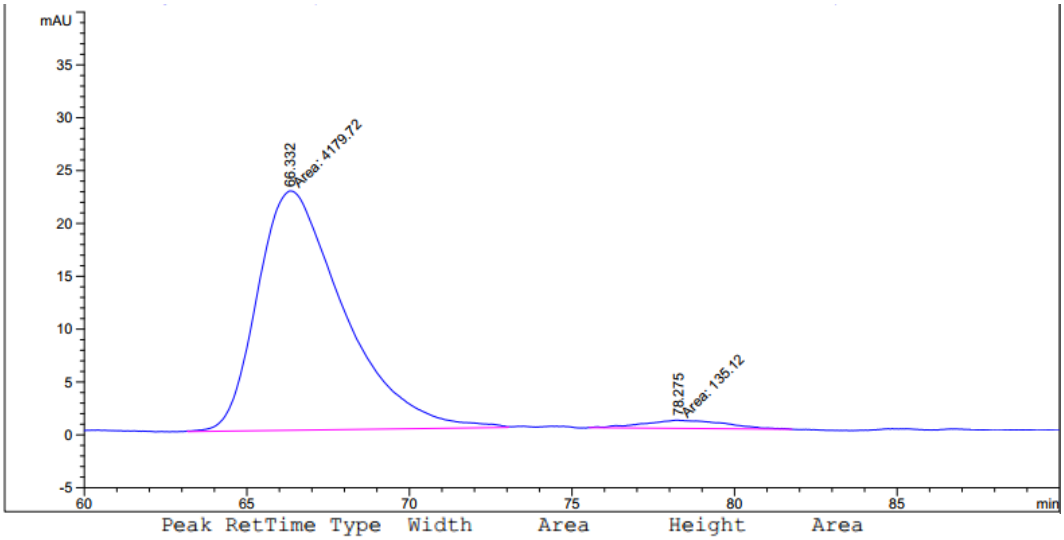
MP: [118-120] °C


OH
S
N
PhthN
Me
3.3f
^{1}H (500 MHz, $CDCl_3$)


OH
S
N
PhthN
Me
3.3f
^{13}C (125 MHz, $CDCl_3$)

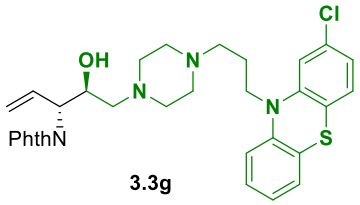


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	69.470	MM	3.0613	3130.54517	17.04343	50.0198
2	80.690	MM	3.5493	3128.07153	14.68869	49.9802



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	66.332	MM	3.0769	4179.72021	22.64035	96.8685
2	78.275	MM	2.9204	135.11977	7.71122e-1	3.1315

2-((3*R*,4*S*)-5-(4-(3-(2-chloro-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-hydroxypent-1-en-3-yl)isoindoline-1,3-dione (3.3g)



3.3g

Alcohol 3.**2g** (80.8 mg, 0.2 mmol) was subjected to standard reaction conditions with 7.5 mol% catalyst (100 °C, 48 h). Upon flash column chromatography (SiO_2, 100% EtOAc), the title compound 3.**3g** (68.3 mg, 0.116 mmol, >20:1 dr) was obtained as a pale yellow solid in 58% yield.

TLC (SiO_2) R_f = 0.3 (100% EtOAc)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.12 (dd, *J* = 16.8, 8.0 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.81 (s, 1H), 6.42 – 6.30 (m, 1H), 5.35 – 5.24 (m, 2H), 4.74 (t, *J* = 7.3 Hz, 1H), 4.30 (dd, *J* = 13.4, 7.0 Hz, 1H), 3.86 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 2H), 2.48 – 2.27 (m, 10H), 2.00 – 1.79 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.4, 146.6, 144.6, 134.3, 133.3, 132.5, 131.9, 128.0, 127.6, 127.5, 124.9, 123.6, 123.0, 122.4, 119.6, 115.9, 77.2, 66.4, 61.2, 57.9, 55.4, 53.2, 45.4, 24.1.

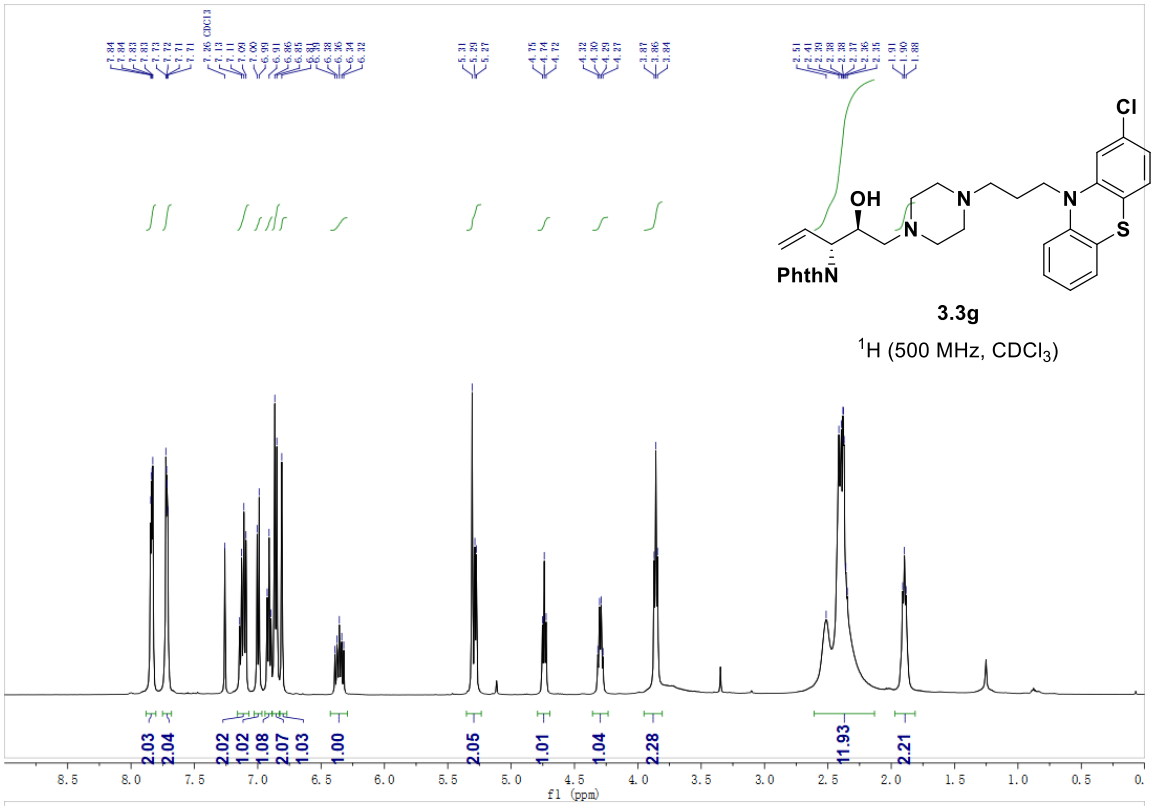
HRMS (H+, *m/z*) for $C_{32}H_{33}ClN_4O_3S$: calcd. = 589.2035; found = 589.2038.

FTIR (neat): 3452, 2940, 2815, 1769, 1708, 1566, 1458, 1382, 1127, 749.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 9:1, 1.0 mL/min, 230 nm) ee = 98%.

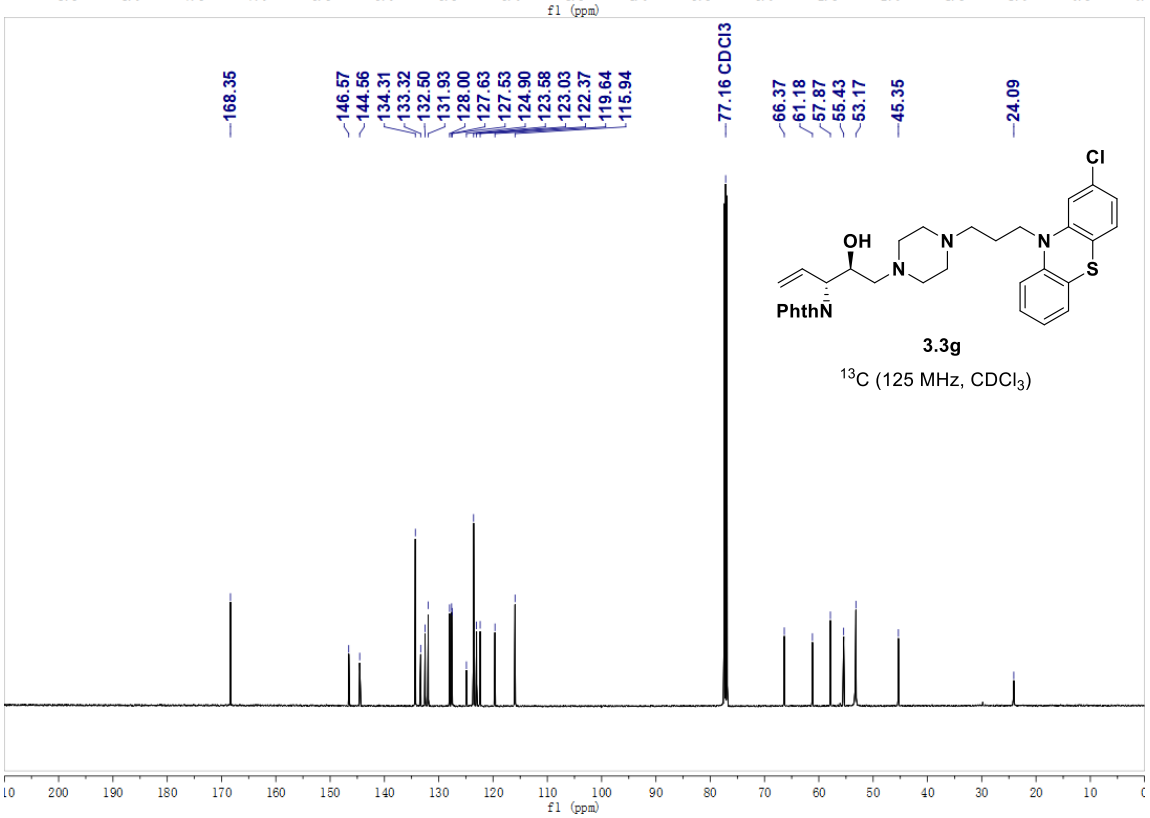
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +34.0° (c = 0.80, $CHCl_3$).

MP: [63-66] °C



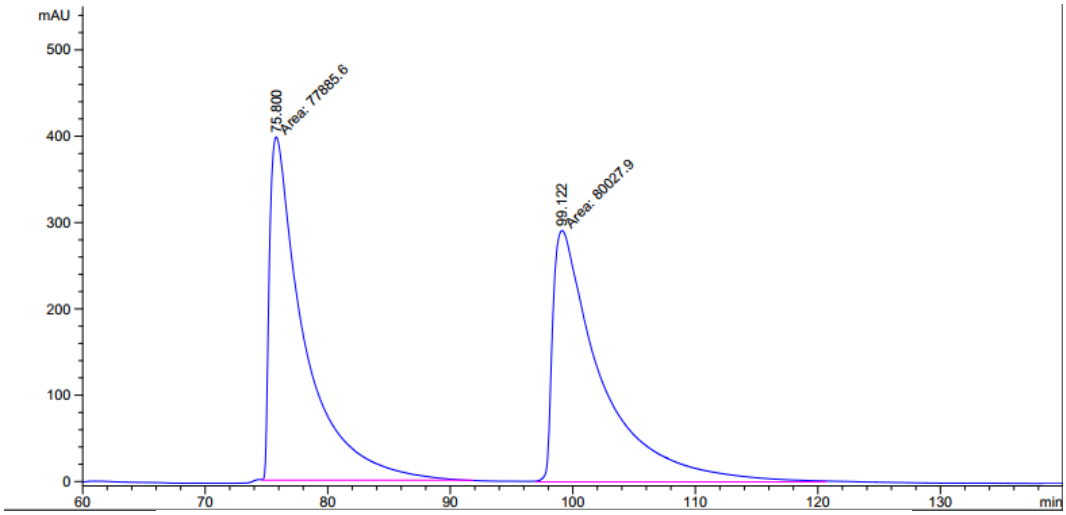
3.3g

^{1}H (500 MHz, $CDCl_3$)

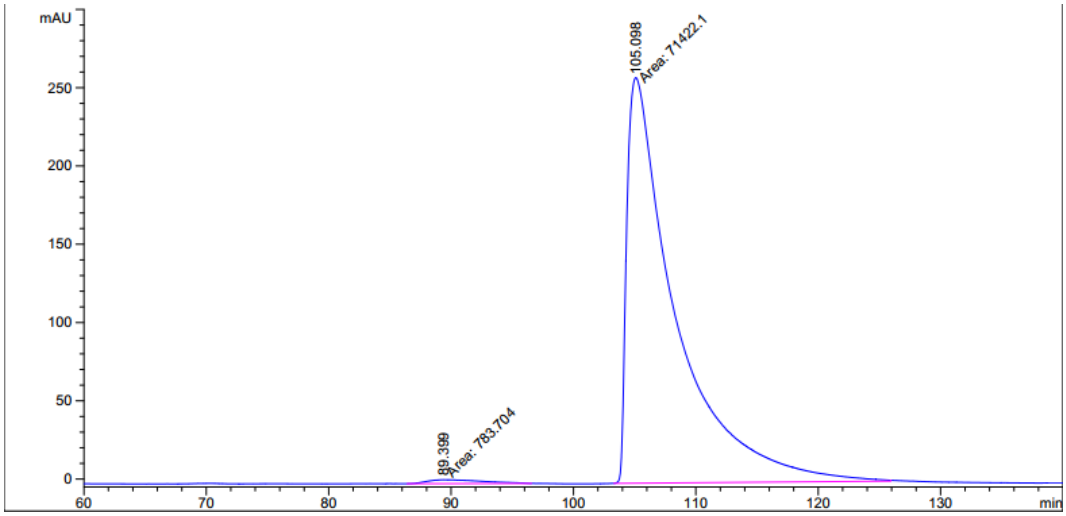


3.3g

^{13}C (125 MHz, $CDCl_3$)

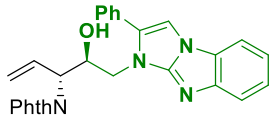


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	75.800	MM	3.2654	7.78856e4	397.53497	49.3217
2	99.122	MM	4.5815	8.00279e4	291.12387	50.6783



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	89.399	MM	5.2784	783.70435	2.47459	1.0854
2	105.098	MM	4.5953	7.14221e4	259.04156	98.9146

2-((3*R*,4*S*)-4-hydroxy-5-(2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-1-yl)pent-1-en-3-yl)isoindoline-1,3-dione (3.3h)



3.3h

Alcohol **3.2h** (55.4 mg, 0.2 mmol) was subjected to standard reaction conditions with 7.5 mol% catalyst (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:Toluene), the title compound **3.3h** (52.7 mg, 0.114 mmol, >20:1 dr) was obtained as a pale yellow solid in 57% yield.

TLC (SiO_2) R_f = 0.38 (30:70 EtOAc:Toluene)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 – 7.70 (m, 4H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.24 – 7.22 (m, 3H), 7.18 – 7.11 (m, 4H), 6.31 (ddd, *J* = 17.4, 10.3, 7.2 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 4.84 – 4.81 (m, 1H), 4.72 (t, *J* = 7.7 Hz, 1H), 4.23 – 4.12 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 134.2, 133.9, 133.2, 131.7, 129.4, 129.1, 128.8, 127.8, 127.3, 123.5, 123.4, 119.5, 119.2, 118.2, 110.3, 103.5, 70.9, 55.9, 48.6.

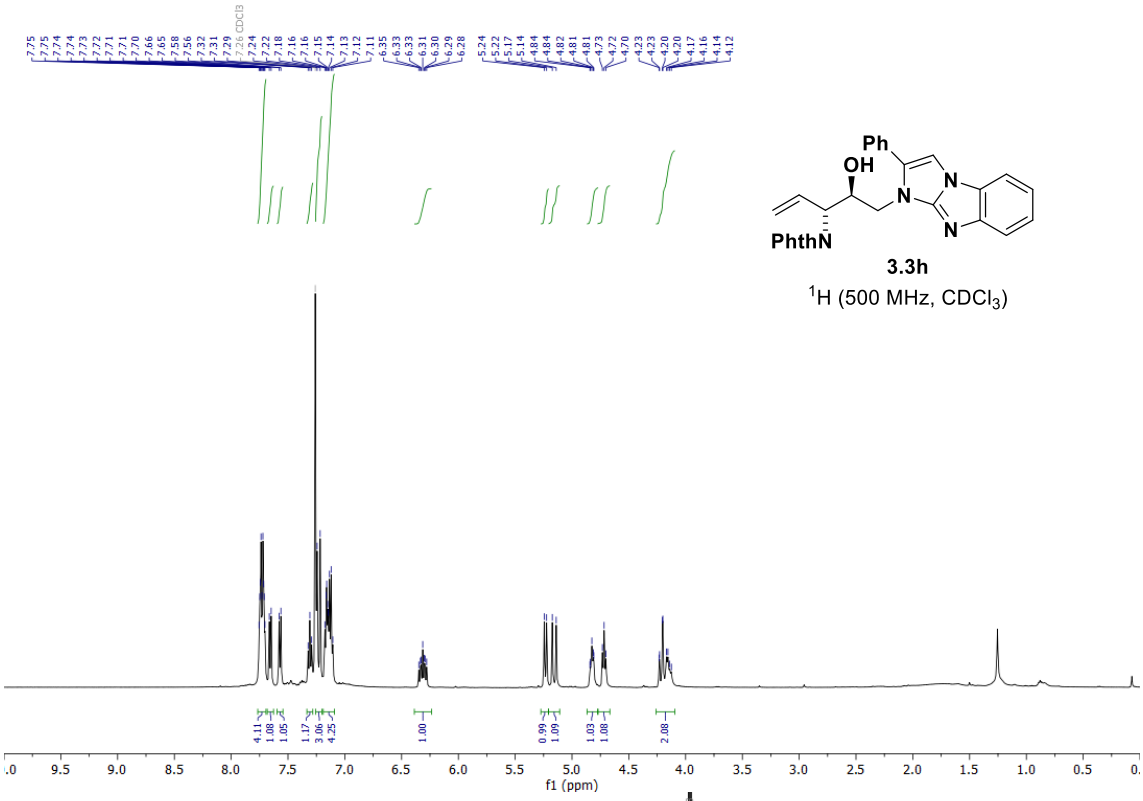
HRMS (Na+, *m/z*) for $C_{28}H_{22}N_4O_3$: calcd. = 485.1584; found = 485.1592.

FTIR (neat): 2922, 1708, 1635, 1558, 1380, 1239, 1066, 740, 718.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 90:10, 1.0 mL/min, 230 nm) ee = 98%.

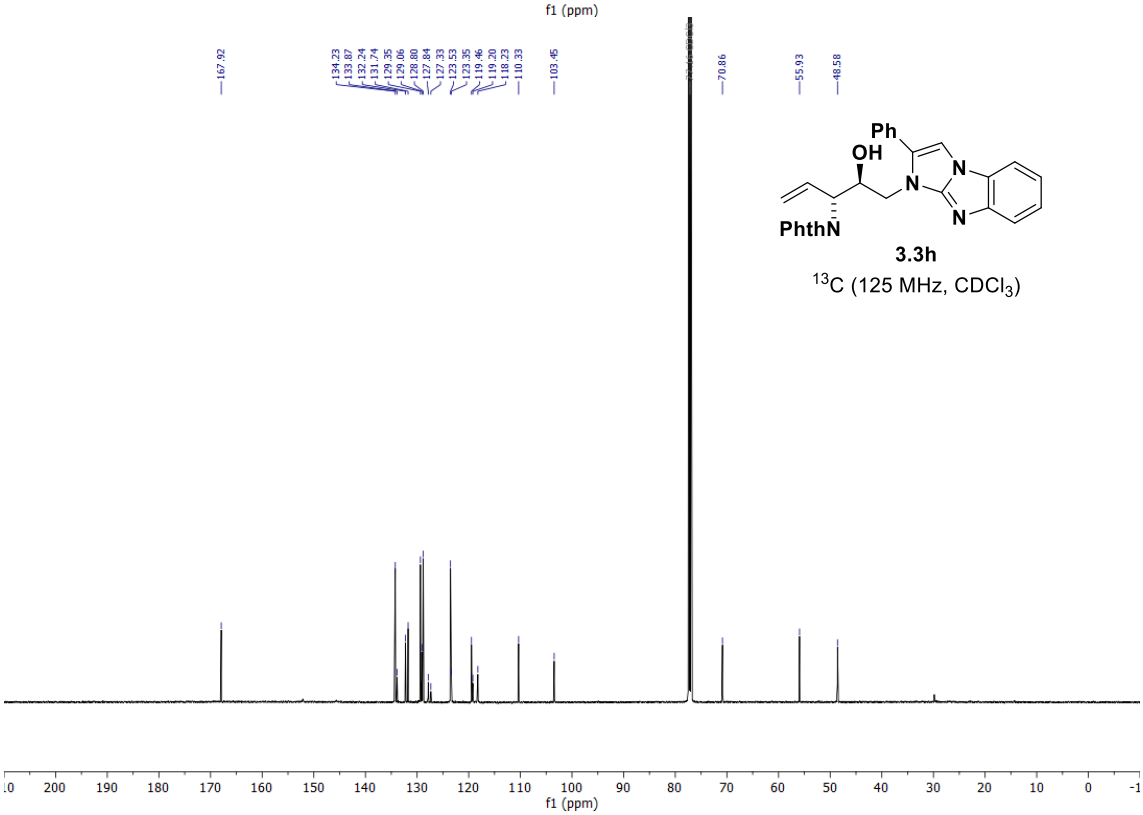
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +3.4° (c = 1.18, $CHCl_3$).

MP [63 – 65] °C



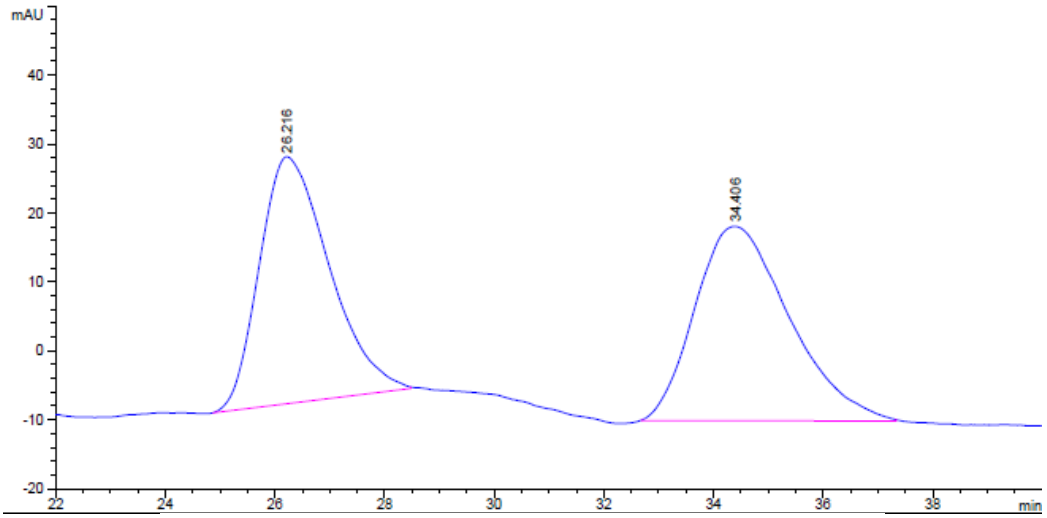
3.3h

^{1}H (500 MHz, $CDCl_3$)



3.3h

^{13}C (125 MHz, $CDCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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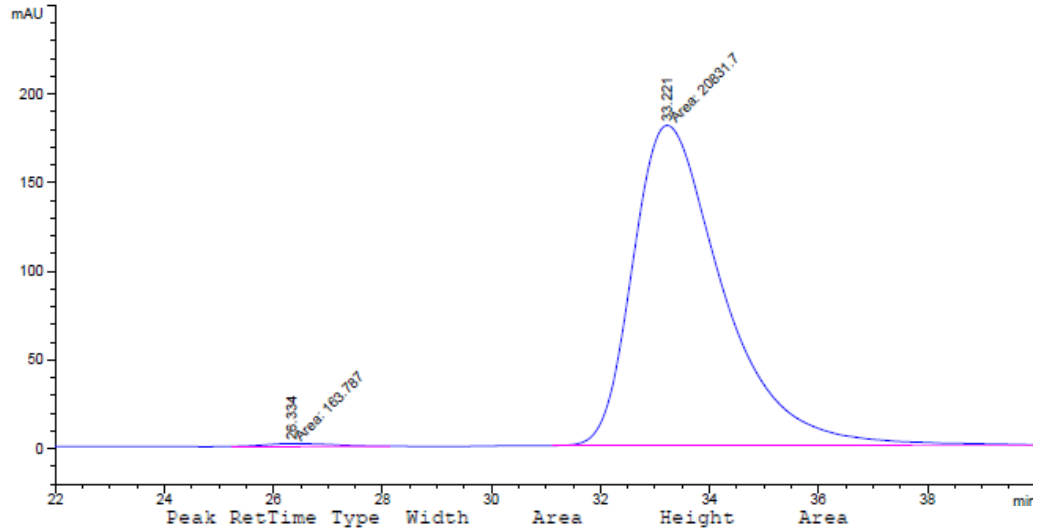
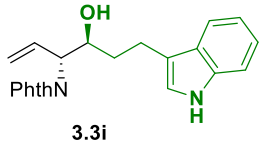
2	34.406	BB	1.4265	3376.83398	28.21054	51.5760



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.334	MM	1.5118	163.78746	1.80560	0.7801
2	33.221	MM	1.9236	2.08317e4	180.48880	99.2199

2-((3*R*,4*S*,*E*)-7-(benzyloxy)-4-hydroxyhepta-1,5-dien-3-yl)isoindoline-1,3-dione (3i)



3.3i

Alcohol **3.2i** (35.0 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) with 7.5 mol% Ir-**VI**. Upon flash column chromatography (SiO_2, 30:80 EtOAc:hexanes), the title compound **3.3i** (53.9 mg, 0.15 mmol, >20:1 dr) was obtained as a yellow solid in 75% yield.

TLC (SiO_2) R_f = 0.28 (30:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.06 (dd, *J* = 11.0, 3.9 Hz, 1H), 7.00 (s, 1H), 6.30 (ddd, *J* = 17.9, 10.3, 7.7 Hz, 1H), 5.34 – 5.23 (m, 2H), 4.75 (dd, *J* = 7.7, 3.8 Hz, 1H), 4.17 – 4.12 (m, 1H), 3.01 (td, *J* = 8.8, 4.3 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.06 – 1.90 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 136.5, 134.4, 131. 8, 131.3, 127.5, 123.7, 122.0, 121.6, 120.1, 119.3, 119.1, 115.9, 111.2, 77.2, 71.8, 59.6, 34.7, 21.4.

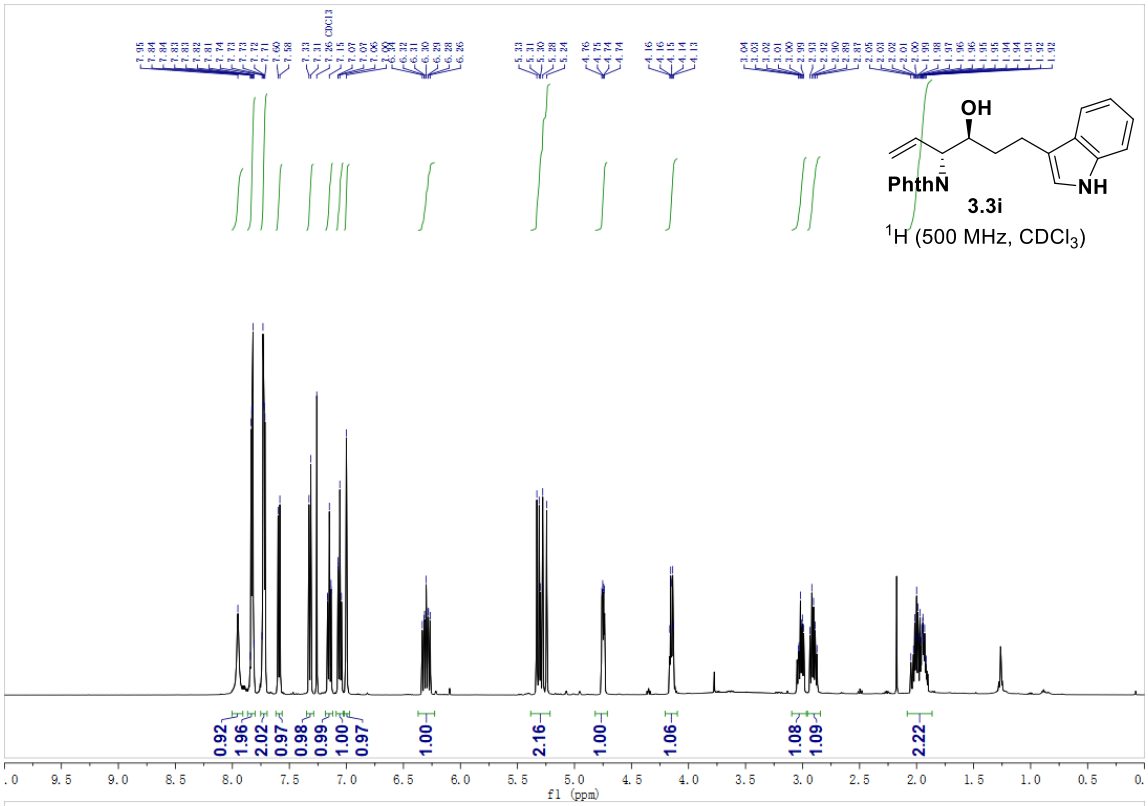
HRMS (Na+, *m/z*) for $C_{22}H_{20}N_2O_3$: calcd. = 383.1366; found = 383.1376.

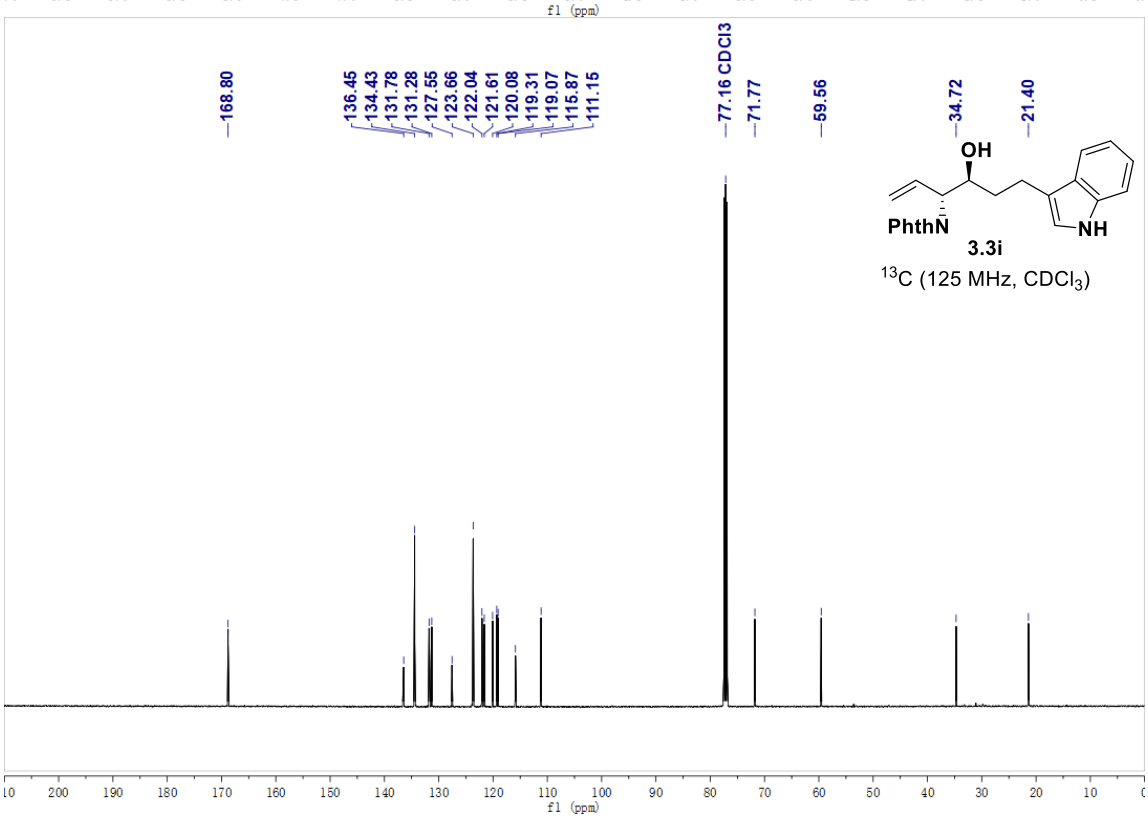
FTIR (neat): 3335, 1708, 1639, 1274, 1263, 764, 734, 703.

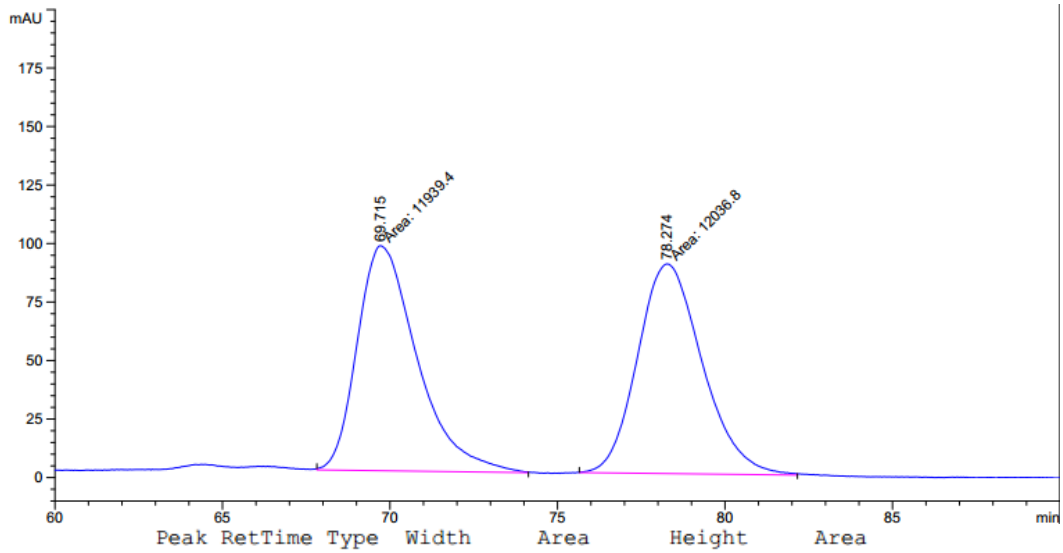
HPLC: (Chiralcel column ADH, Hexane:2-PrOH = 90:10, 1.0 mL/min, 230 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 68.0° (c = 0.37, $CHCl_3$).

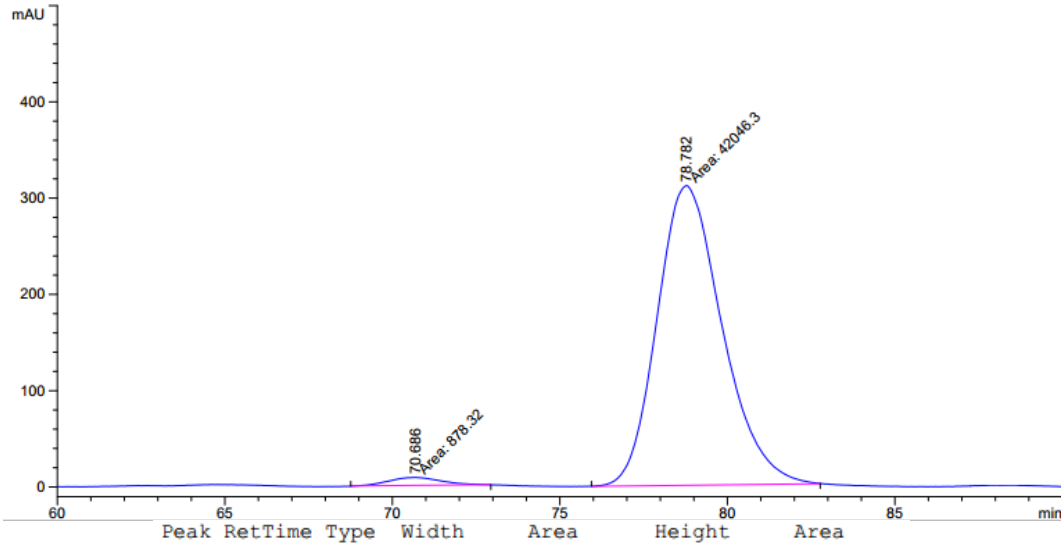
MP : 80-85 °C


OH
PhthN
NH
3.3i
^{1}H (500 MHz, $CDCl_3$)
0.92
1.96
2.02
0.97
0.98
0.99
1.00
0.97
1.00
2.16
1.00
1.06
1.08
1.09
2.22
f1 (ppm)


168.80
136.45
134.43
131.78
131.28
127.55
123.66
122.04
121.61
120.08
119.31
119.07
115.87
111.15
77.16 CDCl3
71.77
59.56
34.72
21.40
OH
PhthN
NH
3.3i
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

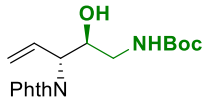


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	69.715	MM	2.0699	1.19394e4	96.13758	49.7969
2	78.274	MM	2.2381	1.20368e4	89.63525	50.2031



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	70.686	MM	1.7774	878.31970	8.23615	2.0462
2	78.782	MM	2.2519	4.20462e4	311.18958	97.9538

***tert*-butyl((2*S*,3*R*)-3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypent-4-en-1-yl)carbamate (3.3j)**



3.3j

Alcohol **3.2j** (32.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3j** (45.1 mg, 0.13 mmol, >20:1 dr) was obtained as a pale yellow oil in 66% yield.

TLC (SiO_2) R_f = 0.32 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.27 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 5.31 (d, *J* = 17.1 Hz, 1H), 4.97 (brs, 1H), 4.76 – 4.74 (m, 1H), 4.25 (brs, 1H), 3.86 (brs, 1H), 3.46 – 3.40 (m, 1H), 3.15 – 3.10 (m, 1H), 1.43 (brs, 9H).

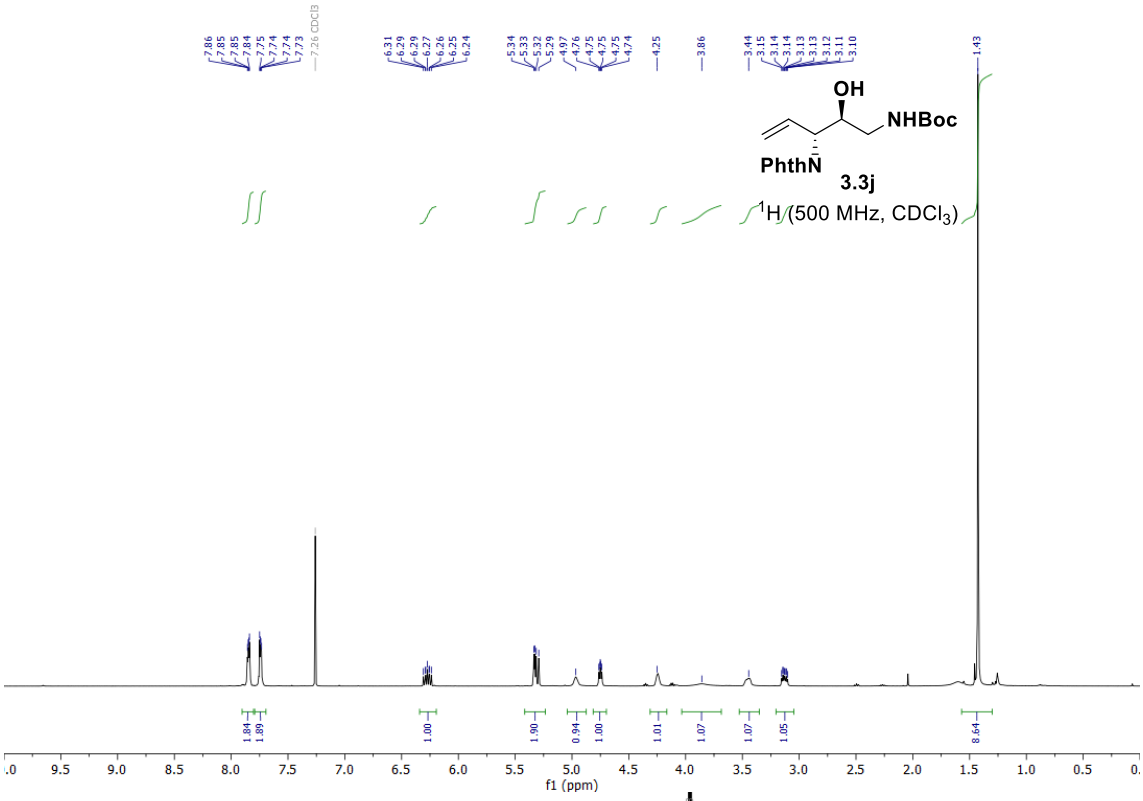
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5 (2C), 156.7, 134.5 (2C), 131.8 (2C), 131.4, 123.7 (2C), 120.4, 79.9, 71.3, 56.8, 43.6, 28.5 (3C).

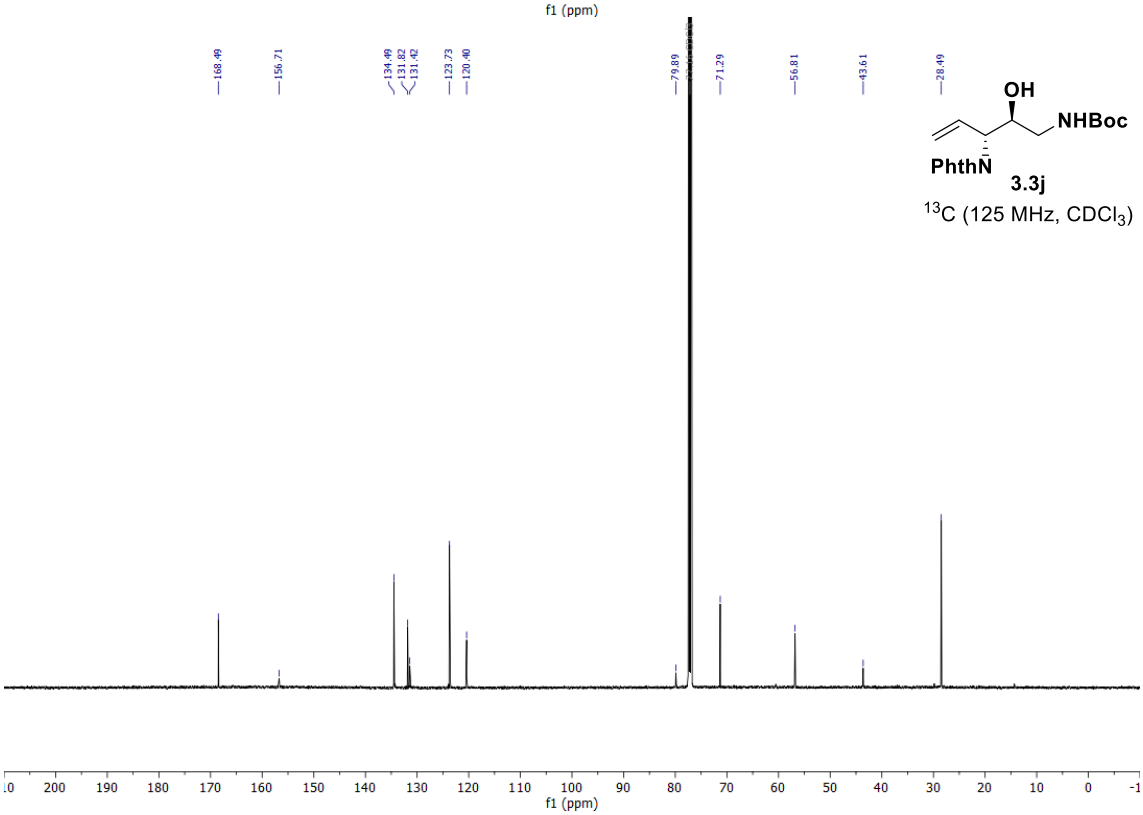
HRMS (Na+, *m/z*) for $C_{18}H_{22}N_2O_5$: calcd. = 369.1421; found = 369.1427.

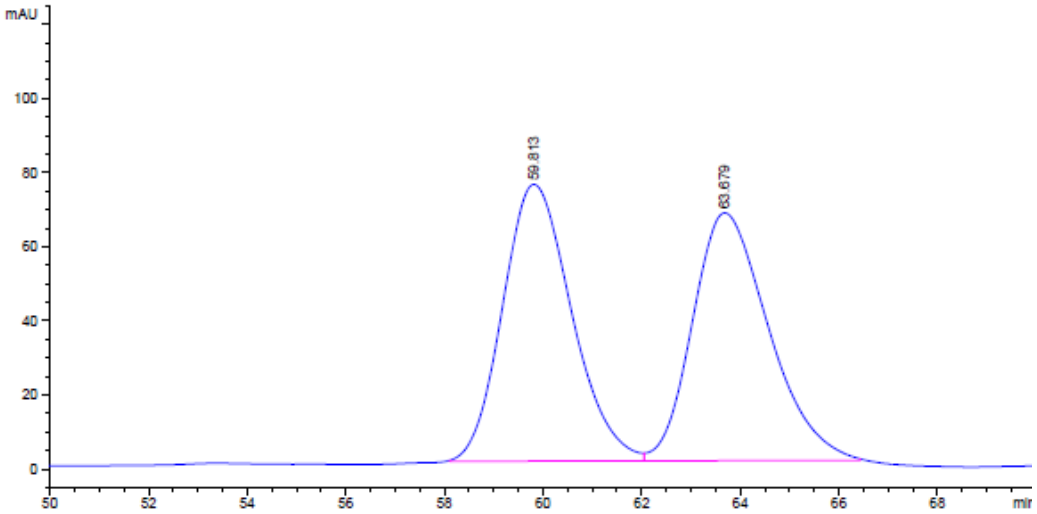
FTIR (neat): 3372, 2978, 1704, 1513, 1381, 1165, 1060

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 97%.

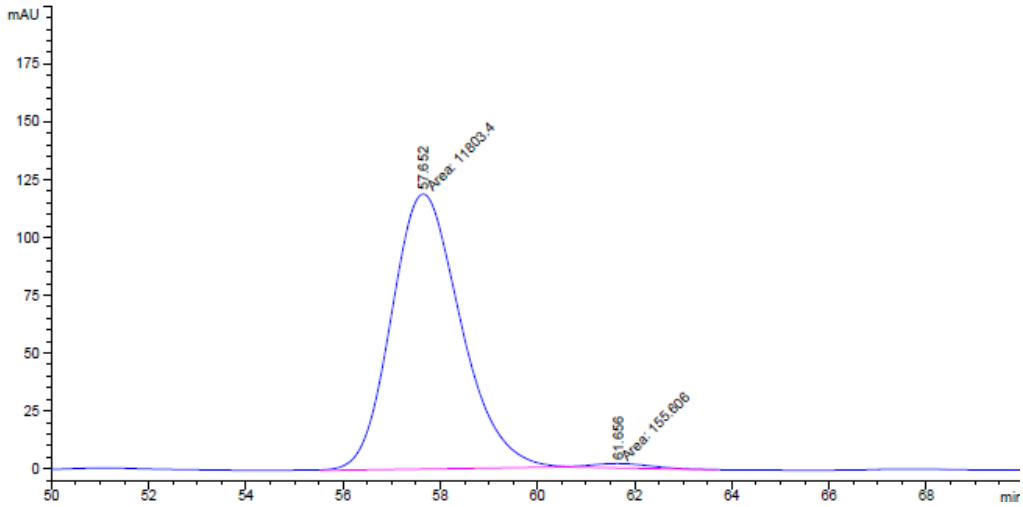
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +30.6° (c = 0.98, $CHCl_3$).


OH
NHBoc
PhthN
3.3j
^{1}H (500 MHz, CDCl$_3$)
f1 (ppm)


OH
NHBoc
PhthN
3.3j
^{13}C (125 MHz, CDCl$_3$)
f1 (ppm)

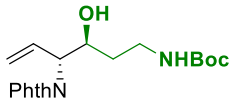


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	59.813	BV	1.4024	7249.68799	74.69029	50.3267
2	63.679	VB	1.4085	7155.55469	66.86340	49.6733



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	57.652	MM	1.6554	1.18034e4	118.84019	98.6988
2	61.656	MM	1.3738	155.60645	1.88773	1.3012

***tert*-butyl((3*S*,4*R*)-4-(1,3-dioxoisoindolin-2-yl)-3-hydroxyhex-5-en-1-yl)carbamate (3.3k)**



3.3k

Alcohol **3.2k** (35.0 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 40:60 EtOAc:hexanes), the title compound **3.3k** (43.2 mg, 0.12 mmol, >20:1 dr) was obtained as a pale yellow oil in 60% yield.

TLC (SiO_2) R_f = 0.29 (50:50 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 3.2 Hz, 2H), 7.77 – 7.69 (m, 2H), 6.35 – 6.22 (m, 1H), 5.28 (dd, *J* = 19.2, 13.9 Hz, 2H), 4.97 (s, 1H), 4.70 – 4.63 (m, 1H), 4.22 – 4.16 (m, 2H), 3.42 (s, 1H), 3.17 (dd, *J* = 13.0, 5.1 Hz, 1H), 1.73 – 1.56 (m, 2H), 1.41 (s, 9H).

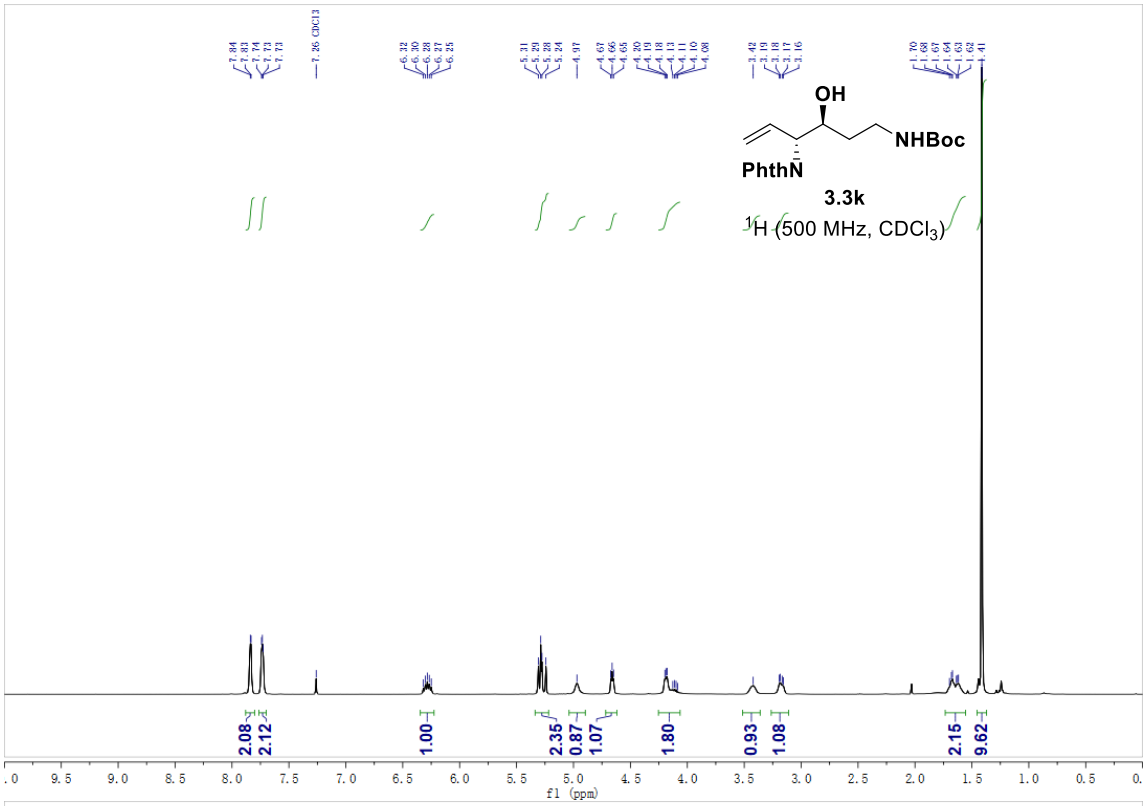
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 156.7, 134.4, 131.8, 123.7, 120.0, 79.5, 70.0, 59.4, 37.6, 34.4, 28.5.

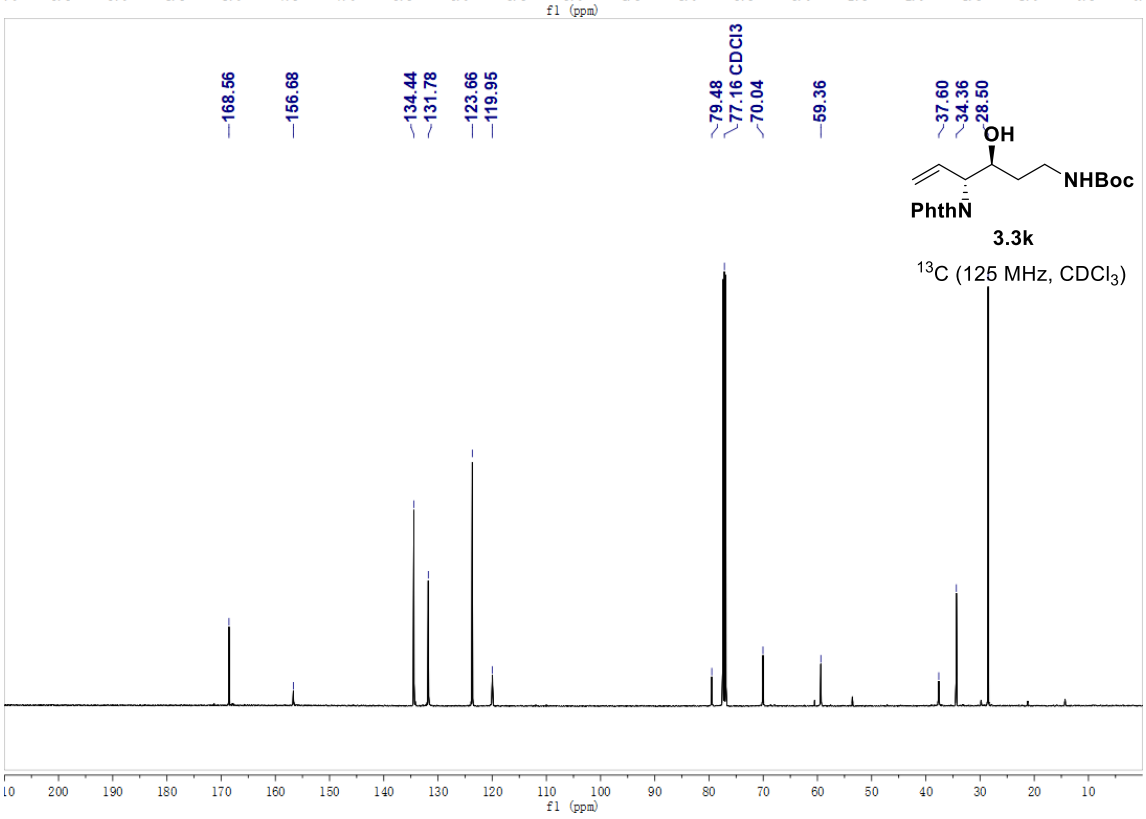
HRMS (H+, *m/z*) for $C_{19}H_{24}N_2O_5$: calcd. = 361.1758; found = 361.1756.

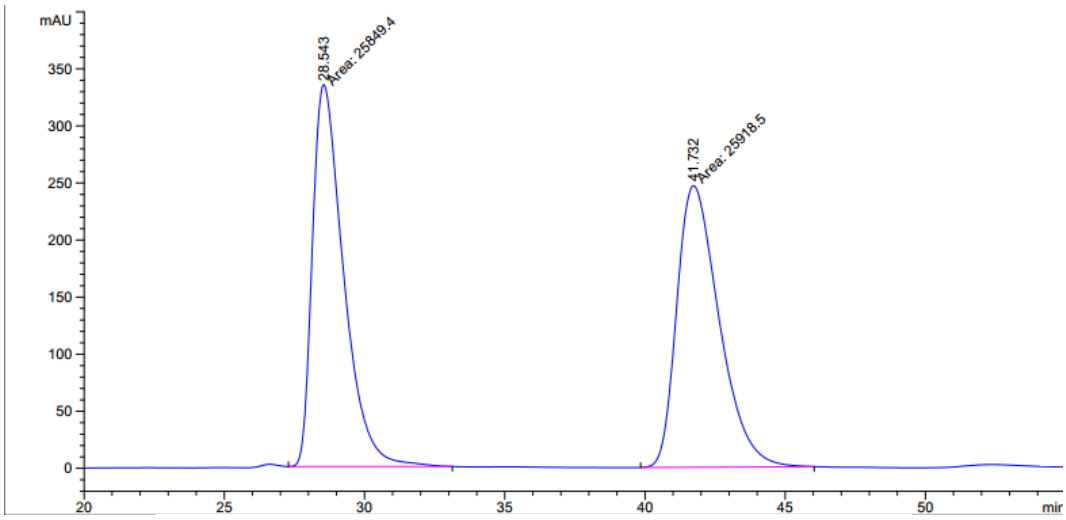
FTIR (neat): 3363, 2360, 2340, 1635, 1274, 1263, 763, 748.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 94%.

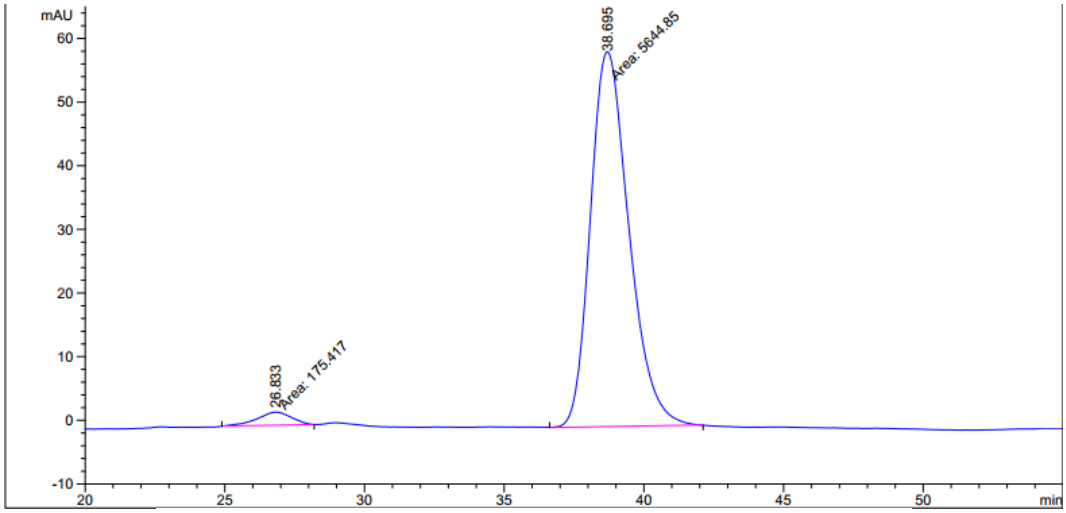
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +44.9° (c = 0.67, $CHCl_3$).


OH
NHBoc
PhthN
3.3k
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


168.56
156.68
134.44
131.78
123.66
119.95
79.48
77.16 CDCl3
70.04
59.36
37.60
34.36
28.50
OH
NHBoc
PhthN
3.3k
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

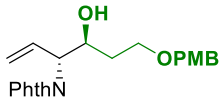


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.543	MM	1.2876	2.58494e4	334.60706	49.9333
2	41.732	MM	1.7510	2.59185e4	246.69958	50.0667



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.833	MM	1.4119	175.41704	2.07075	3.0139
2	38.695	MM	1.5974	5644.85156	58.89788	96.9861

2-((3*R*,4*S*)-4-hydroxy-6-((4-methoxybenzyl)oxy)hex-1-en-3-yl)isoindoline-1,3-dione (3.3l)



3.3l

Alcohol Oxidation level: Alcohol **3.2l** (39.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3l** (54.2 mg, 0.142 mmol, >20:1 dr) was obtained as a colorless oil in 71% yield.

Aldehyde Oxidation level: *dehydro*-**3.2l** (38.8 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) with 7.5% catalyst of Ir-**VI** and 300 mol% 2-PrOH (36.0 mg). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3l** (47.3 mg, 0.124 mmol, >20:1 dr) was obtained as a colorless oil in 62% yield.

TLC (SiO_2) R_f = 0.28 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.38 – 6.28 (m, 1H), 5.32 – 5.23 (m, 2H), 4.72 (dd, *J* = 7.0, 6.2 Hz, 1H), 4.46 – 4.39 (m, 2H), 4.35 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.92 (s, 1H), 3.78 (s, 3H), 3.71 – 3.65 (m, 1H), 3.64 – 3.58 (m, 1H), 1.85 – 1.77 (m, 2H).

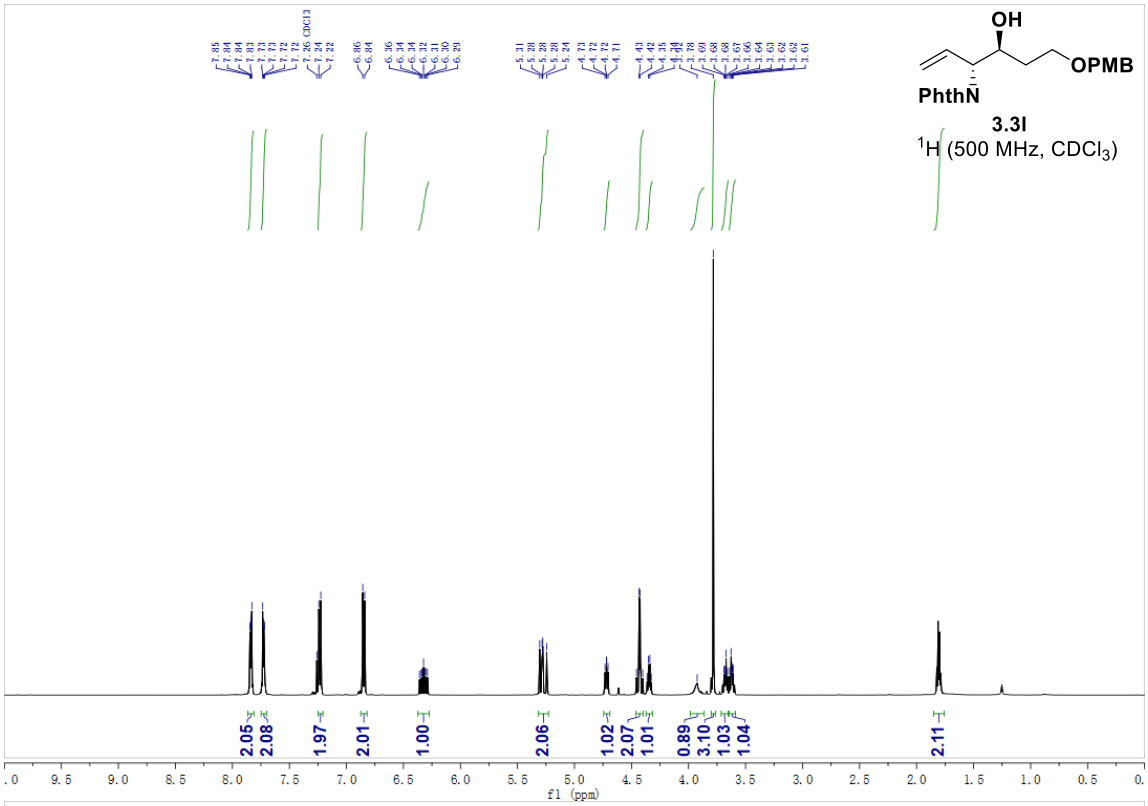
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 159.3, 134.4, 131.9, 130.2, 129.5, 123.6, 123.6, 119.8, 113.9, 77.2, 73.1, 70.6, 67.8, 59.2, 55.4, 33.8.

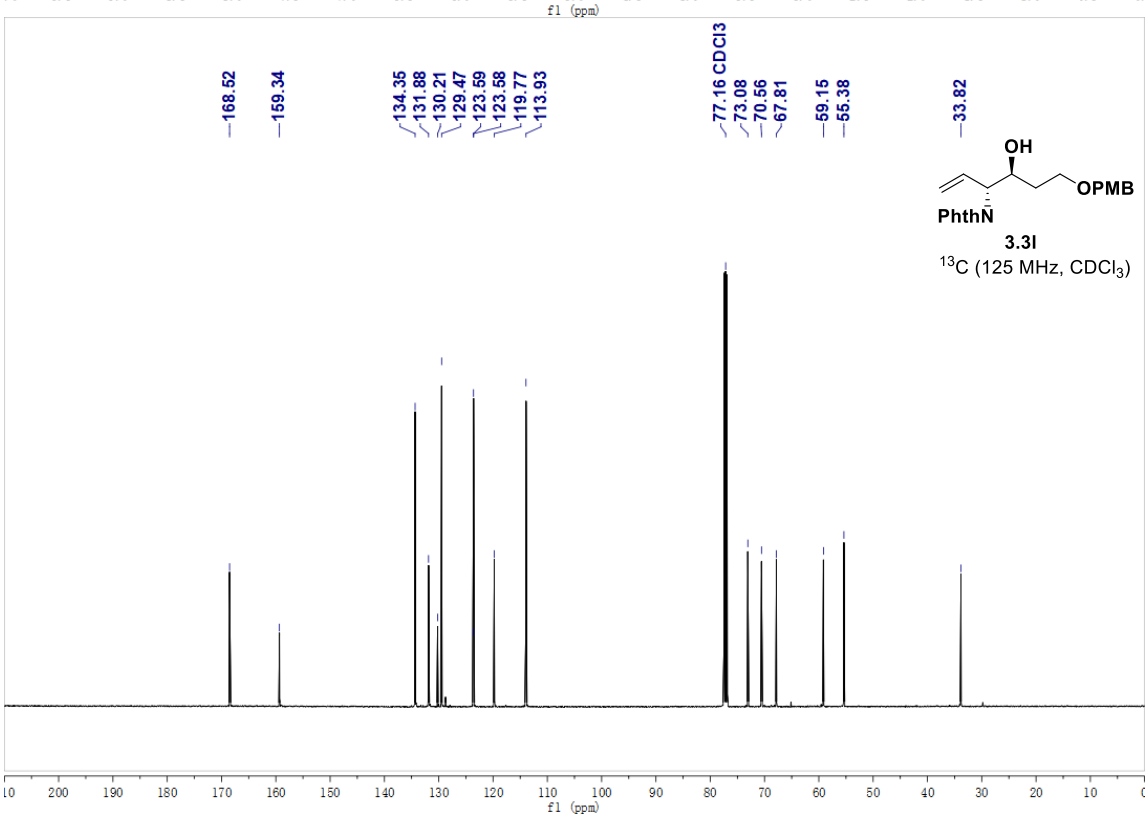
HRMS (Na+, *m/z*) for $C_{22}H_{23}NO_5$: calcd. = 404.1468; found = 404.1476.

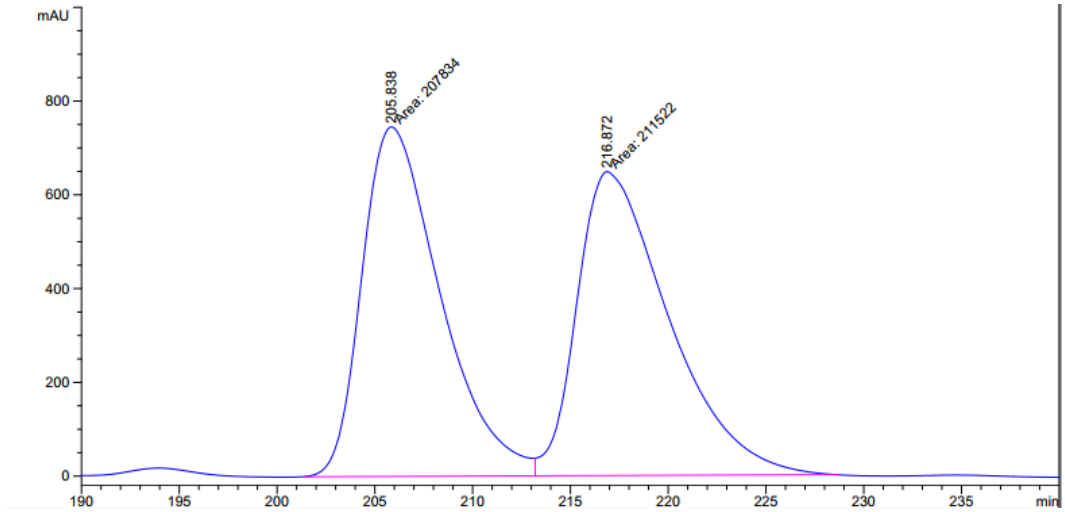
FTIR (neat): 3404, 1770, 1709, 1513, 1382, 1265, 1085, 733, 703.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 96:4, 1.0 mL/min, 230 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +32.5° (c = 0.83, $CHCl_3$).

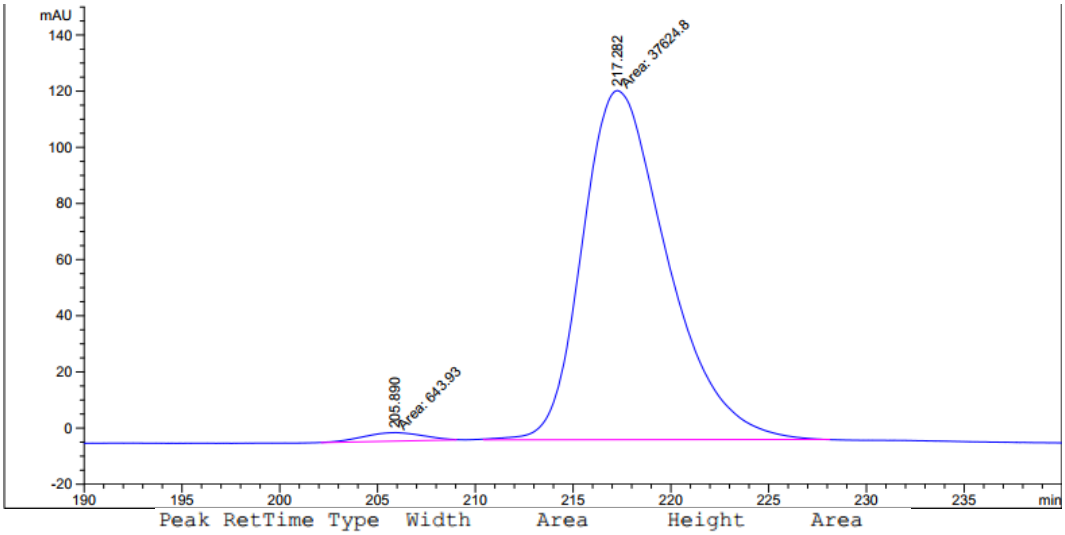

OH
OPMB
PhthN
3.3l
1H (500 MHz, CDCl3)
f1 (ppm)


168.52
159.34
134.35
131.88
130.21
129.47
123.59
123.58
119.77
113.93
77.16 CDCl3
73.08
70.56
67.81
59.15
55.38
33.82
OH
OPMB
PhthN
3.3l
13C (125 MHz, CDCl3)
f1 (ppm)



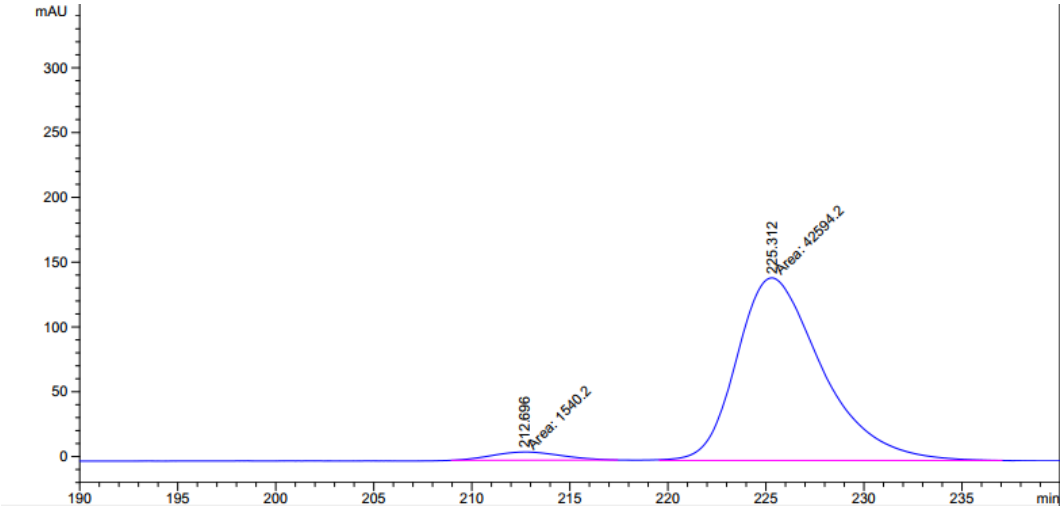
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	205.838	MF	4.6470	2.07834e5	745.40668	49.5603
2	216.872	FM	5.4390	2.11522e5	648.16034	50.4397

Alcohol Oxidation Level:

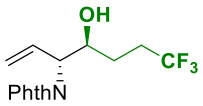


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	205.890	MM	3.5313	643.92981	3.03916	1.6827
2	217.282	MM	5.0435	3.76248e4	124.33395	98.3173

Aldehyde Oxidation Level:



2-((3*R*,4*S*)-7,7,7-trifluoro-4-hydroxyhept-1-en-3-yl)isoindoline-1,3-dione (.33m)



3.3m

Alcohol **3.2m** (25.6 mg, 0.2 mmol) was subjected to standard reaction conditions with 7.5% mol of (*R*)-**Ir-VI** (100 °C, 48 h). Upon flash column chromatography (SiO_2, 15:85 EtOAc:hexanes), the title compound **3.3m** (47.0 mg, 0.15 mmol, >20:1 dr) was obtained as a white solid in 75% yield.

TLC (SiO_2) R_f = 0.28 (15:85 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.32 – 6.18 (m, 1H), 5.46 – 5.26 (m, 2H), 4.67 (dd, *J* = 8.0, 3.8 Hz, 1H), 4.21 – 4.00 (m, 1H), 3.80 (s, 1H), 2.57 – 2.33 (m, 1H), 2.27 – 2.10 (m, 1H), 1.83 – 1.72 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.6, 131.7, 130.6, 123.8, 121.1, 77.2, 70.8, 59.6, 30.34 (q, *J* = 29.0 Hz), 26.8, 26.8.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -66.4 (t, *J* = 10.9 Hz).

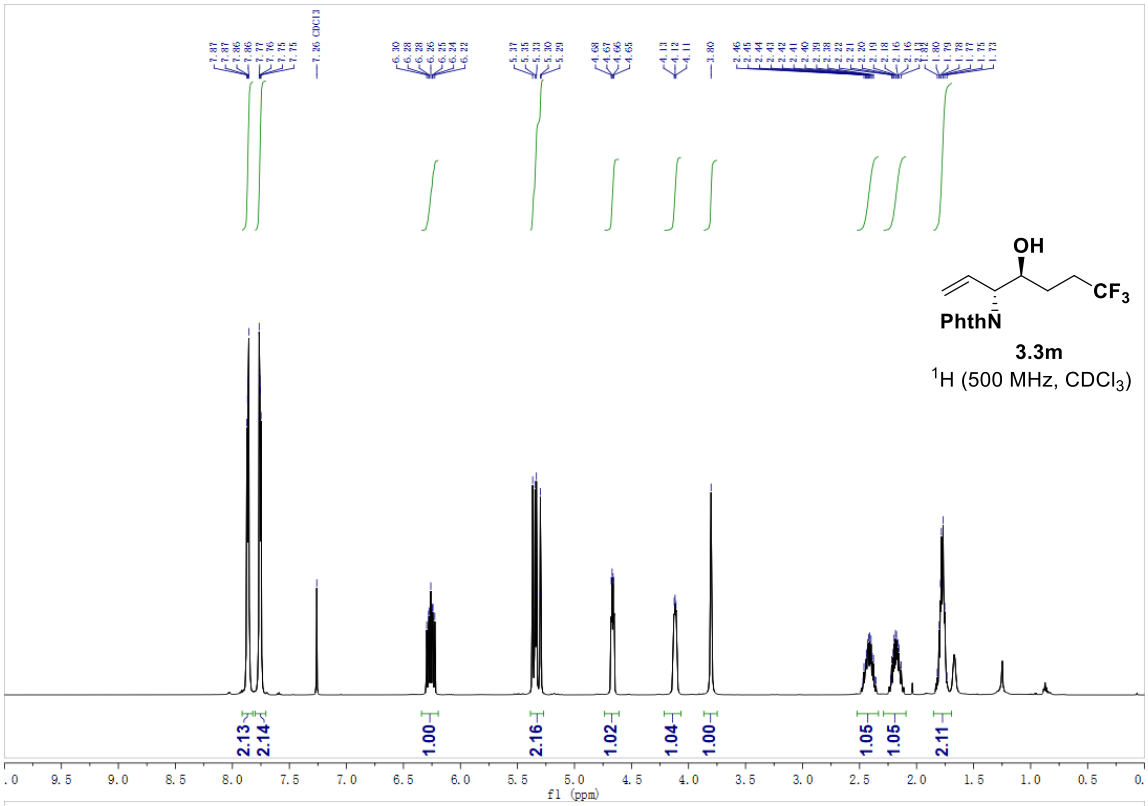
HRMS (H+, *m/z*) for $C_{15}H_{14}F_3NO_3$: calcd. = 314.0999; found =314.1001.

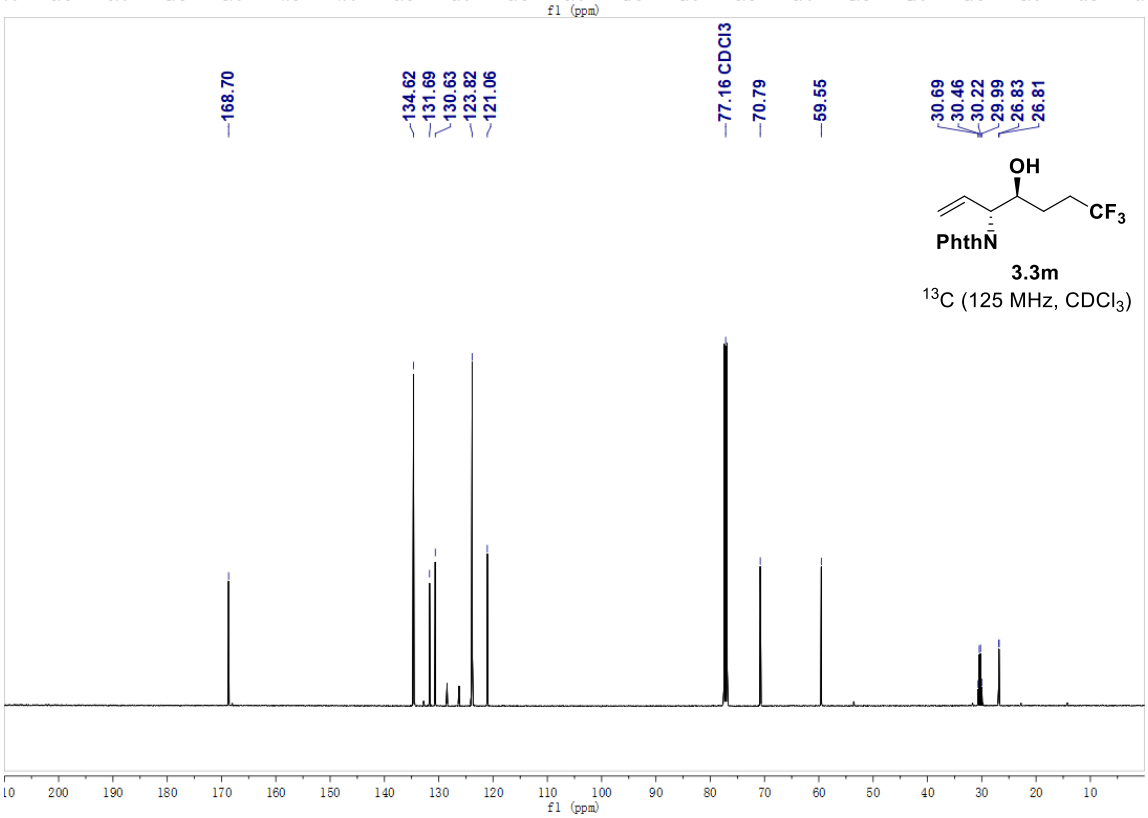
FTIR (neat): 3346, 2360, 2341, 1704, 1382, 1275, 1137, 749.

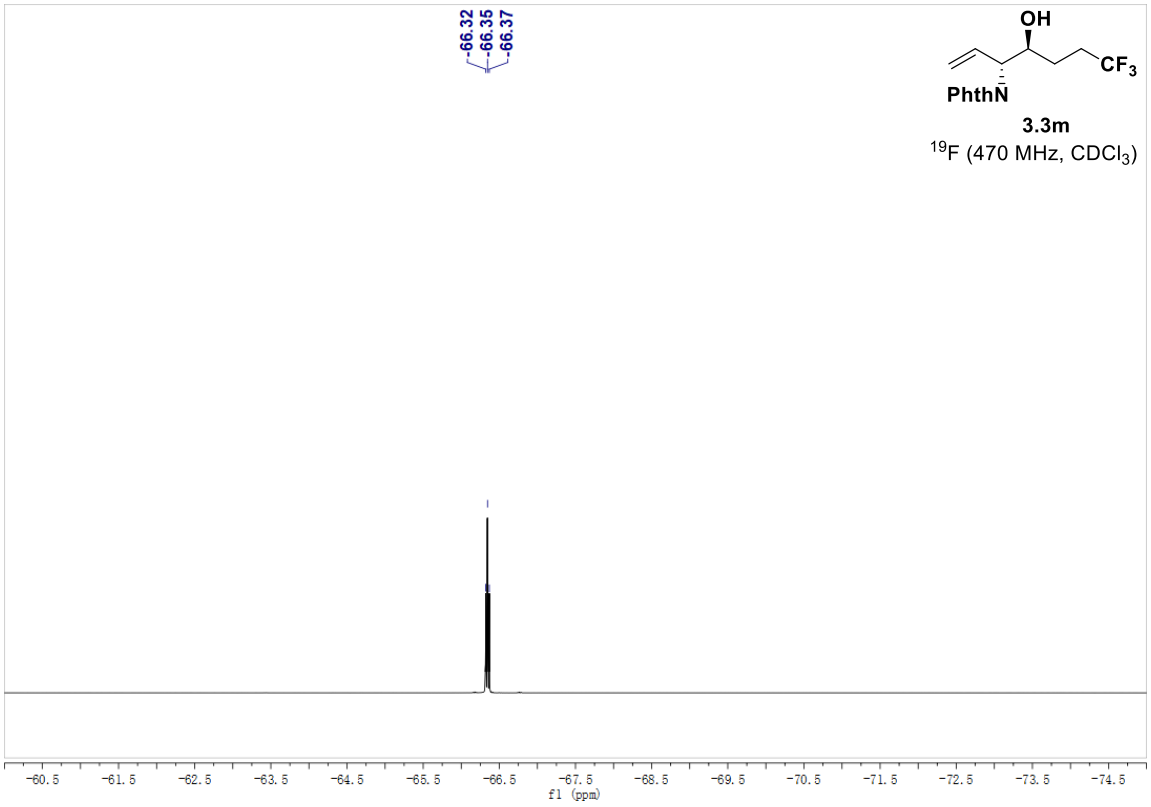
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 97:3, 1.0 mL/min, 230 nm) ee = 94%.

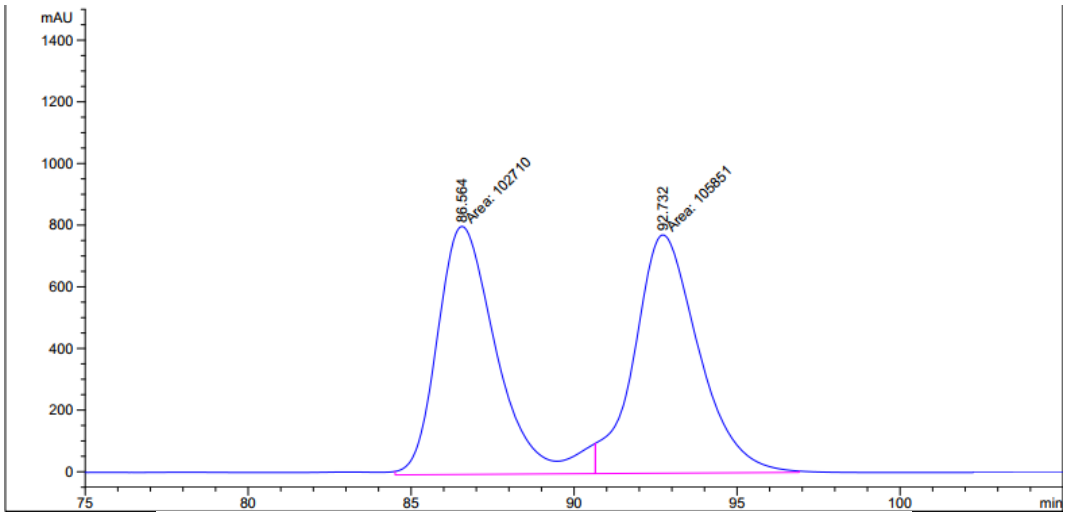
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +40.5° (c = 0.74, $CHCl_3$).

MP [60 – 64] °C

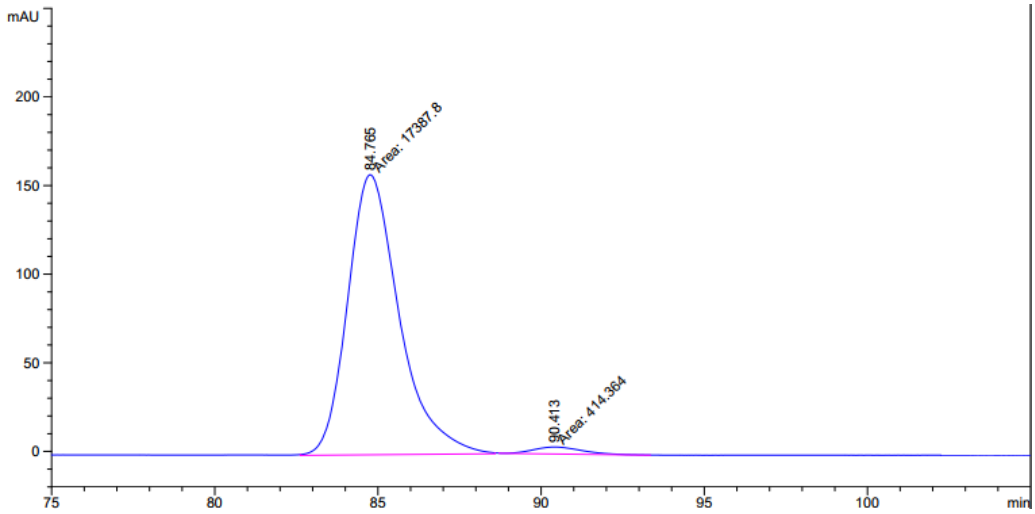

OH
CF3
PhthN
3.3m
1H (500 MHz, CDCl3)
2.13
2.14
1.00
2.16
1.02
1.04
1.00
1.05
1.05
2.11
f1 (ppm)


168.70
134.62
131.69
130.63
123.82
121.06
77.16 CDCl3
70.79
59.55
30.69
30.46
30.22
29.99
26.83
26.81
OH
CF3
PhthN
3.3m
13C (125 MHz, CDCl3)
f1 (ppm)


-66.32
-66.35
-66.37
OH
CF3
PhthN
3.3m
19F (470 MHz, CDCl3)
-60.5
-61.5
-62.5
-63.5
-64.5
-65.5
-66.5
-67.5
-68.5
-69.5
-70.5
-71.5
-72.5
-73.5
-74.5
f1 (ppm)

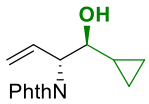


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.564	MF	2.1271	1.02710e5	804.78033	49.2471
2	92.732	FM	2.2819	1.05851e5	773.11945	50.7529



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	84.765	MM	1.8340	1.73878e4	158.01463	97.6724
2	90.413	MM	1.7555	414.36432	3.93394	2.3276

2-((1*S*,2*R*)-1-cyclopropyl-1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione (33.n)



3.3n

Alcohol **3.2n** (14.4 mg, 0.2 mmol) was subjected to standard reaction conditions using 5 mol% of (*R*)-**Ir-V** as catalyst (100 °C, 48 h). Upon flash column chromatography (SiO_2, 40:60 EtOAc:hexanes), the title compound **3.3n** (29.8 mg, 0.16 mmol, >20:1 dr) was obtained as a pale yellow solid in 58% yield.

TLC (SiO_2) R_f = 0.28 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.38 (ddd, *J* = 17.6, 9.9, 7.9 Hz, 1H), 5.32 (dd, *J* = 13.7, 2.3 Hz, 2H), 4.93 – 4.79 (m, 1H), 3.40 (dd, *J* = 8.7, 5.8 Hz, 1H), 3.09 (s, 1H), 1.09 – 0.91 (m, 1H), 0.61 – 0.48 (m, 1H), 0.44 – 0.31 (m, 2H), 0.23 – 0.11 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.4, 132.1, 131.8, 123.6, 120.0, 77.2, 76.3, 59.7, 15.3, 2.6, 2.4.

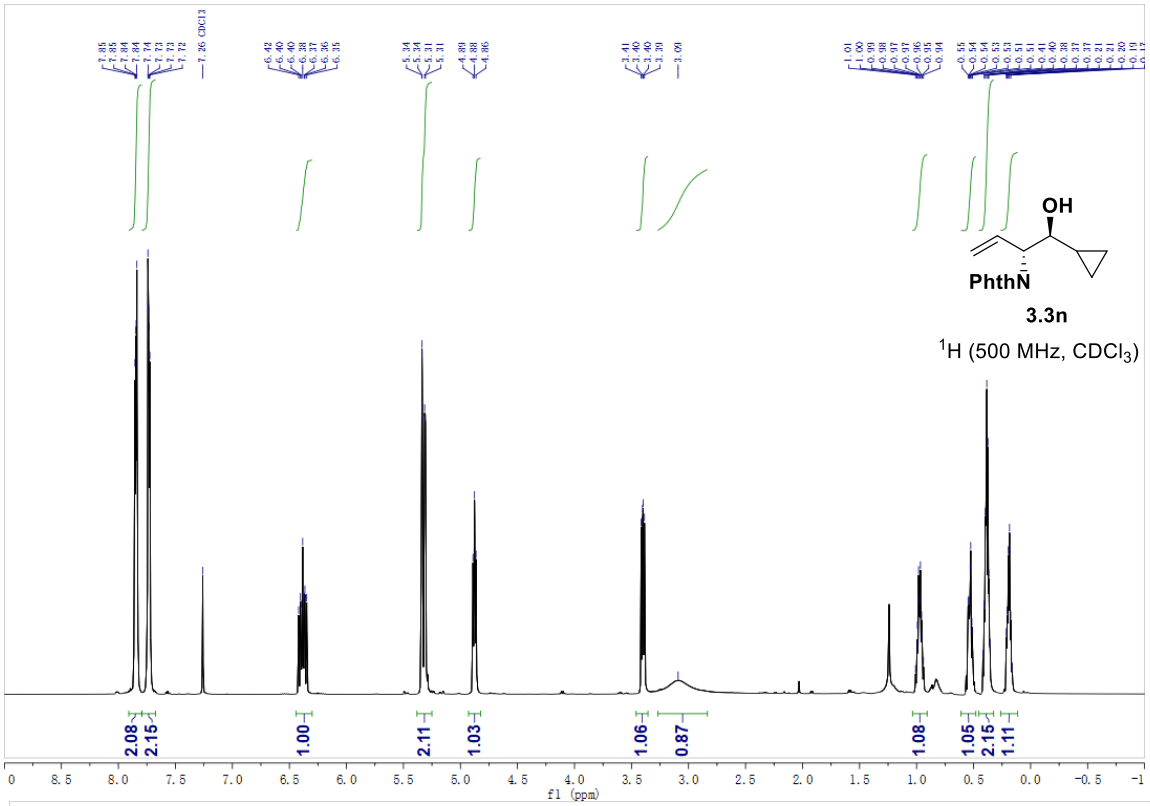
HRMS (Na+, *m/z*) for $C_{15}H_{15}NO_3$: calcd. = 280.0944; found = 280.0946.

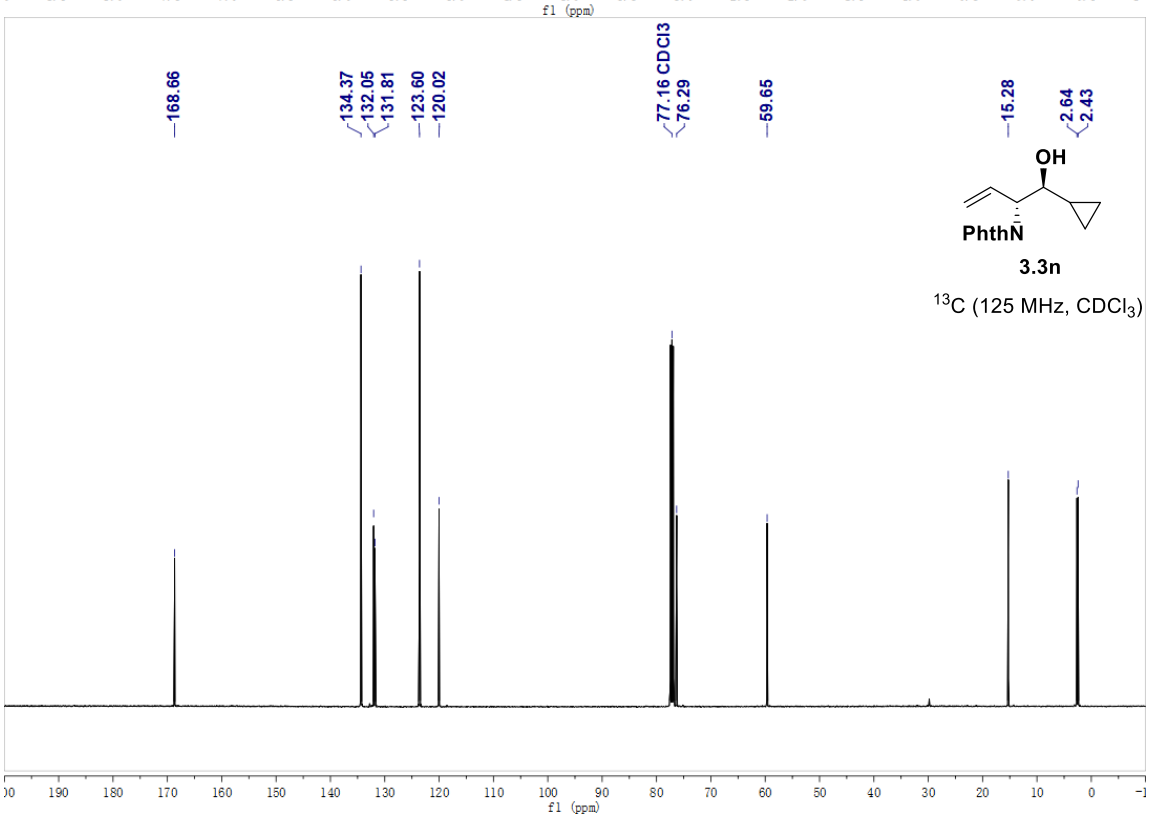
FTIR (neat): 3363, 2359, 2340, 1711, 1264, 1085, 733, 703.

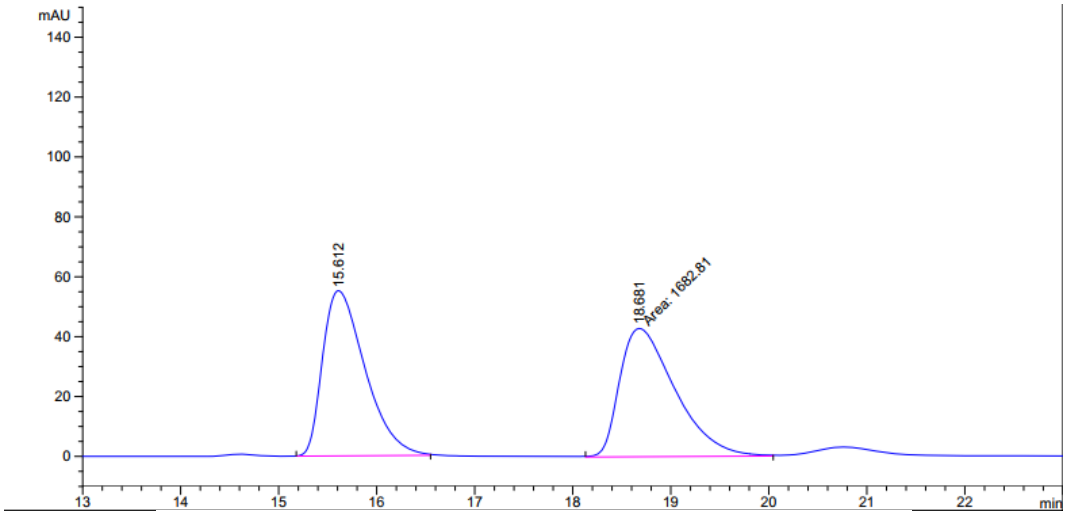
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 96%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +20.4° (c = 1.10, $CHCl_3$).

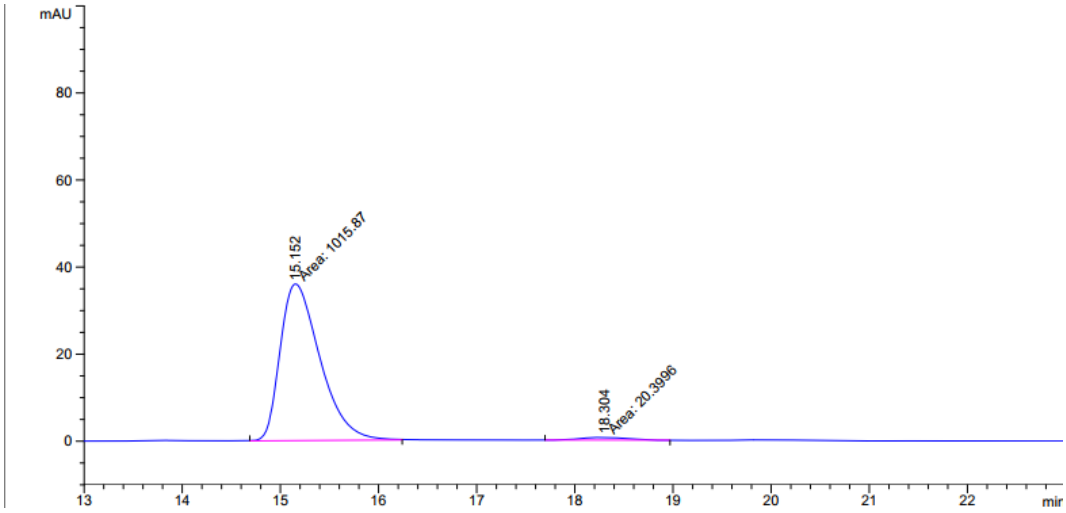
MP [55 – 60] °C


OH
PhthN
3.3n
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


OH
PhthN
3.3n
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

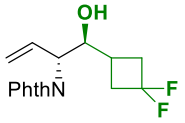


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.612	BB	0.4650	1659.61731	55.16368	49.6531
2	18.681	MM	0.6546	1682.80798	42.84468	50.3469



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.152	MM	0.4708	1015.86859	35.96019	98.0314
2	18.304	MM	0.5429	20.39956	6.26202e-1	1.9686

2-((1*S*,2*R*)-1-cyclopropyl-1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione (3.3o)



3.3o

Alcohol **3.2o** (24.4 mg, 0.2 mmol) was subjected to standard reaction conditions with longer reaction time (100 °C, 72 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3o** (37.5 mg, 0.122 mmol, >20:1 dr) was obtained as a white solid in 61% yield.

TLC (SiO_2) R_f = 0.26 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.26 (ddd, *J* = 17.2, 10.2, 8.2 Hz, 1H), 5.32 (dd, *J* = 20.1, 13.7 Hz, 2H), 4.63 (dd, *J* = 8.1, 4.1 Hz, 1H), 4.06 (d, *J* = 4.2 Hz, 1H), 3.73 (d, *J* = 2.1 Hz, 1H), 2.72 – 2.38 (m, 4H), 2.30 (dd, *J* = 8.0, 3.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 134.6, 134.5, 131. 7, 130.8, 123.8, 123.7, 121.0, 77.2, 73.9, 57.7, 37.3 (m), 36.8 (m), 26.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -82.3 (tt, *J* = 12.0, 5.9 Hz), -82.7 (ddt, *J* = 17.6, 11.9, 5.8 Hz), -96.6 (m), -97.0 (m).

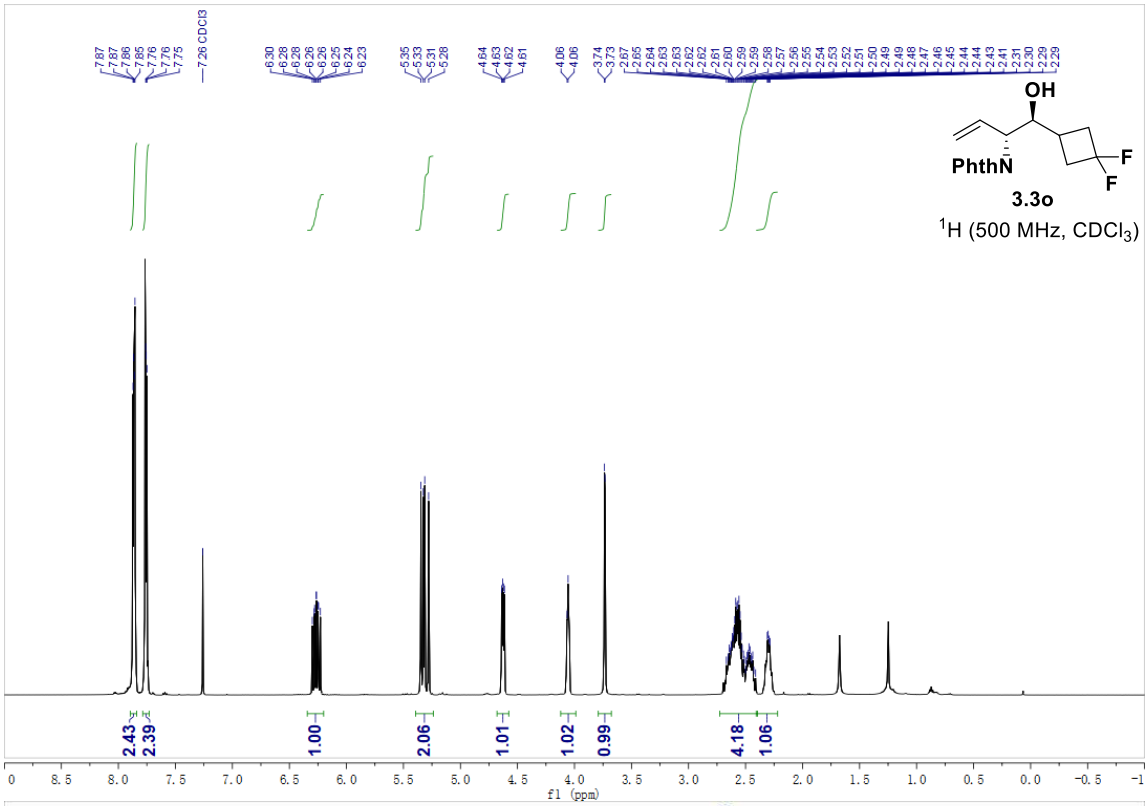
HRMS (Na+, *m/z*) for $C_{16}H_{15}F_2NO_3$: calcd. = 330.0912; found = 330.0916.

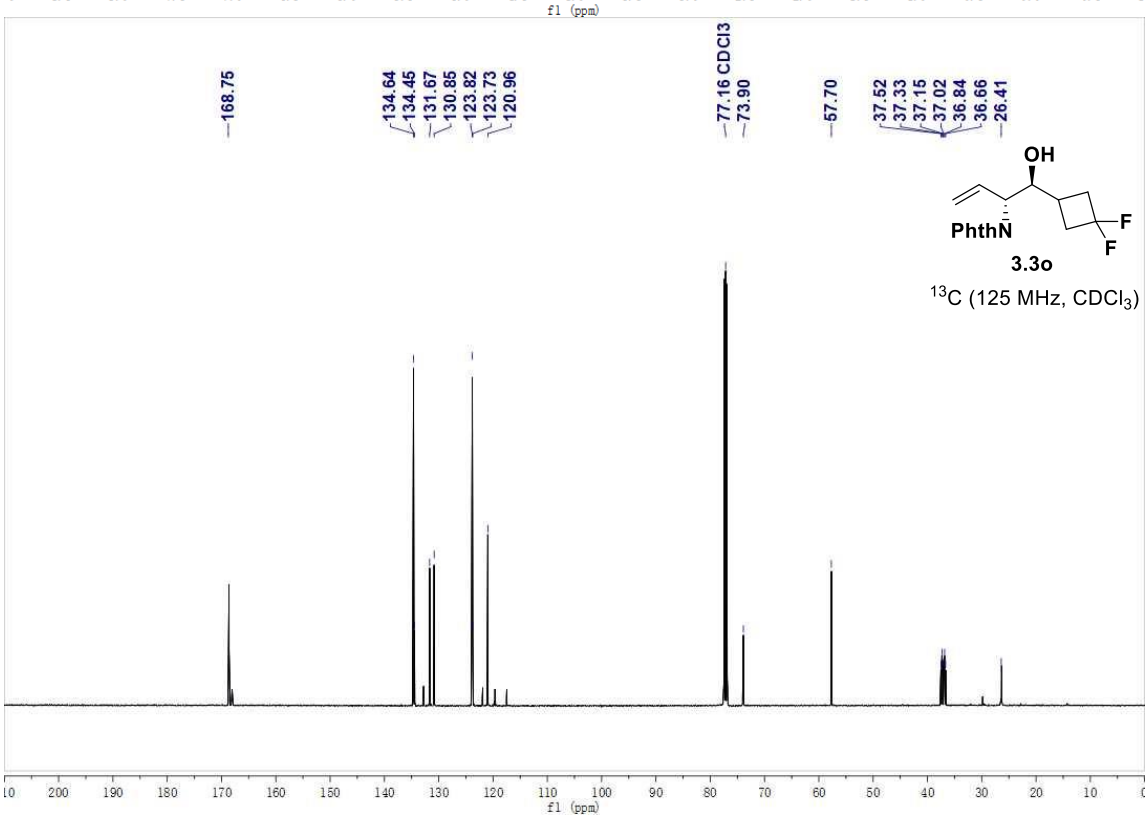
FTIR (neat): 3469, 2631, 2340, 1705, 1382, 1296, 1265, 1070, 763.

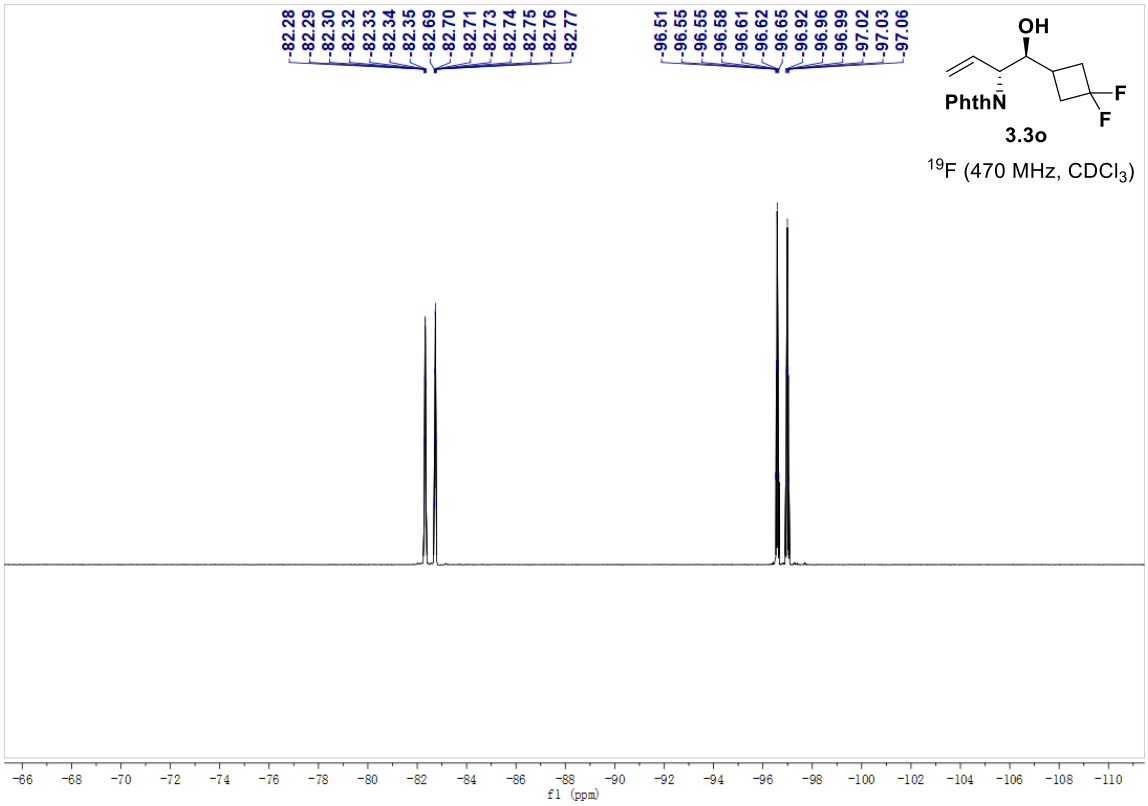
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 94%.

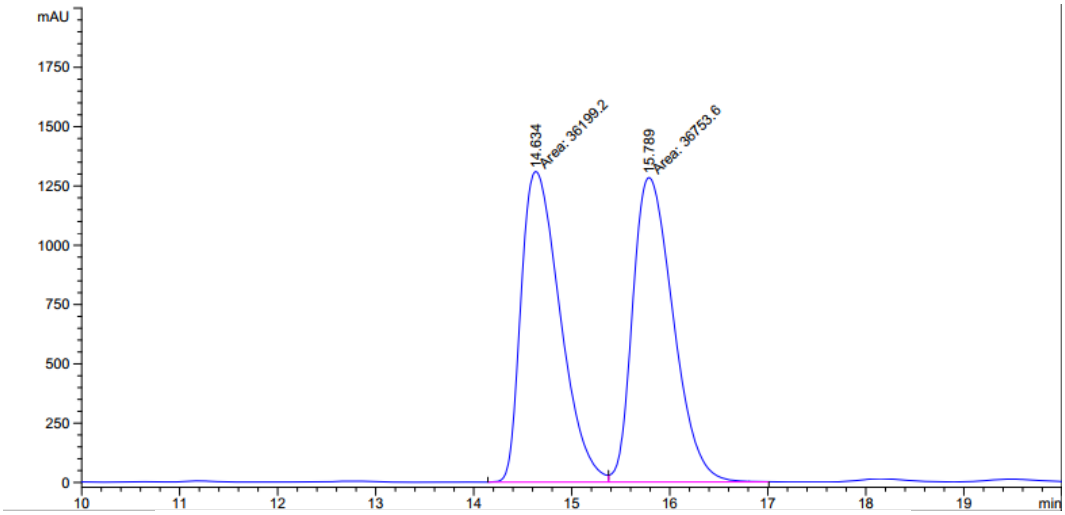
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +14.0° (c = 0.87, $CHCl_3$).

MP [78 – 80] °C

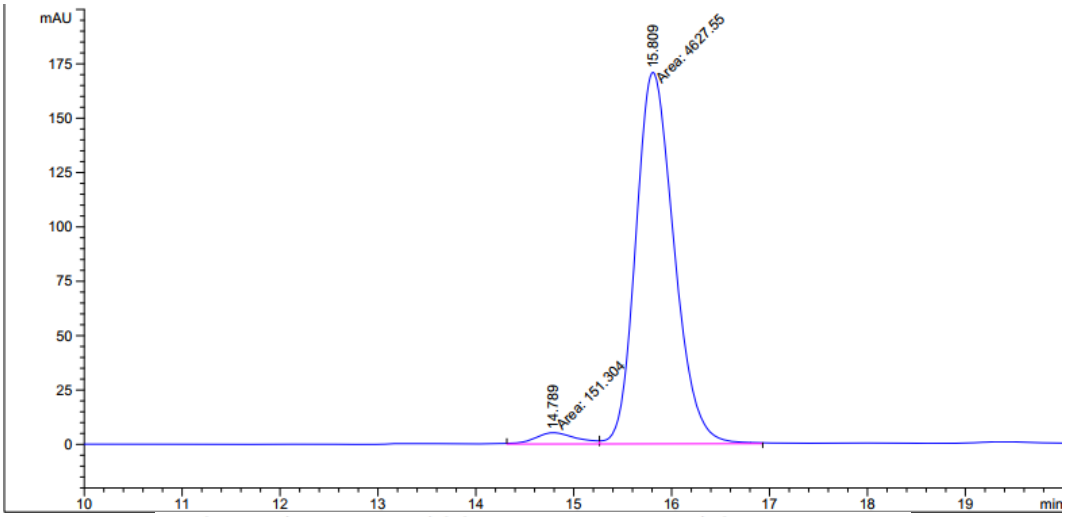

OH
PhthN
F
F
3.3o
^{1}H (500 MHz, $CDCl_3$)
7.87
7.87
7.86
7.85
7.76
7.76
7.75
7.26 CDCl3
6.30
6.28
6.28
6.26
6.26
6.25
6.24
6.23
5.35
5.33
5.31
5.28
4.64
4.63
4.62
4.61
4.06
4.06
3.74
3.73
2.67
2.65
2.64
2.63
2.63
2.62
2.62
2.61
2.60
2.59
2.59
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.45
2.44
2.44
2.43
2.41
2.31
2.30
2.29
2.29
2.43
2.39
1.00
2.06
1.01
1.02
0.99
4.18
1.06
f1 (ppm)


OH
PhthN
F
F
3.3o
^{13}C (125 MHz, $CDCl_3$)
168.75
134.64
134.45
131.67
130.85
123.82
123.73
120.96
77.16 CDCl3
73.90
57.70
37.52
37.33
37.15
37.02
36.84
36.66
26.41
f1 (ppm)


-82.28
-82.29
-82.30
-82.32
-82.33
-82.34
-82.35
-82.69
-82.70
-82.71
-82.73
-82.74
-82.75
-82.76
-82.77
-96.51
-96.55
-96.55
-96.58
-96.61
-96.62
-96.65
-96.92
-96.96
-96.99
-97.02
-97.03
-97.06
OH
PhthN
F
F
3.3o
19F (470 MHz, CDCl3)
-66
-68
-70
-72
-74
-76
-78
-80
-82
-84
-86
-88
-90
-92
-94
-96
-98
-100
-102
-104
-106
-108
-110
f1 (ppm)

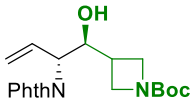


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.634	MF	0.4608	3.61992e4	1309.30823	49.6201
2	15.789	FM	0.4772	3.67536e4	1283.57446	50.3799



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.789	MF	0.4843	151.30403	5.20708	3.1661
2	15.809	FM	0.4515	4627.54736	170.80737	96.8339

***tert*-butyl 3-((1*S*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)-1-hydroxybut-3-en-1-yl)azetidine-1-carboxylate (3.3p)**



3.3p

Alcohol **3.2p** (37.4 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3p** (49.9 mg, 0.134 mmol, >20:1 dr) was obtained as a light yellow solid in 67% yield.

TLC (SiO_2) R_f = 0.20 (30:70 EtOAc:hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.30 – 6.21 (m, 1H), 5.29 (dd, *J* = 26.8, 13.7 Hz, 2H), 4.59 (dd, *J* = 8.1, 3.8 Hz, 1H), 4.18 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.97 – 3.91 (m, 3H), 3.75 (dd, *J* = 8.5, 5.9 Hz, 1H), 2.74 – 2.64 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 156.4, 134.5, 131.6, 130.7, 123.7, 120.8, 79.5, 77.2, 73.7, 57.4, 51.1, 31.8, 28.5.

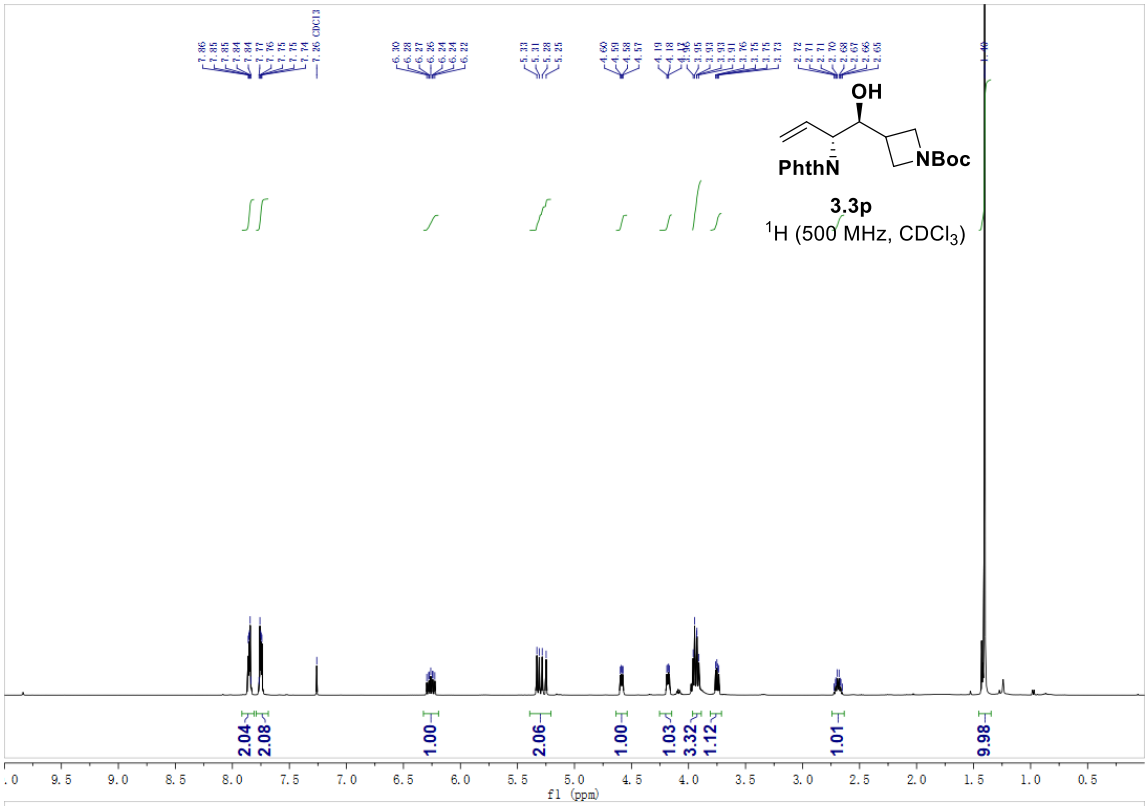
HRMS (K+, *m/z*) for $C_{20}H_{24}N_2O_5$: calcd. = 411.1317; found = 411.1323.

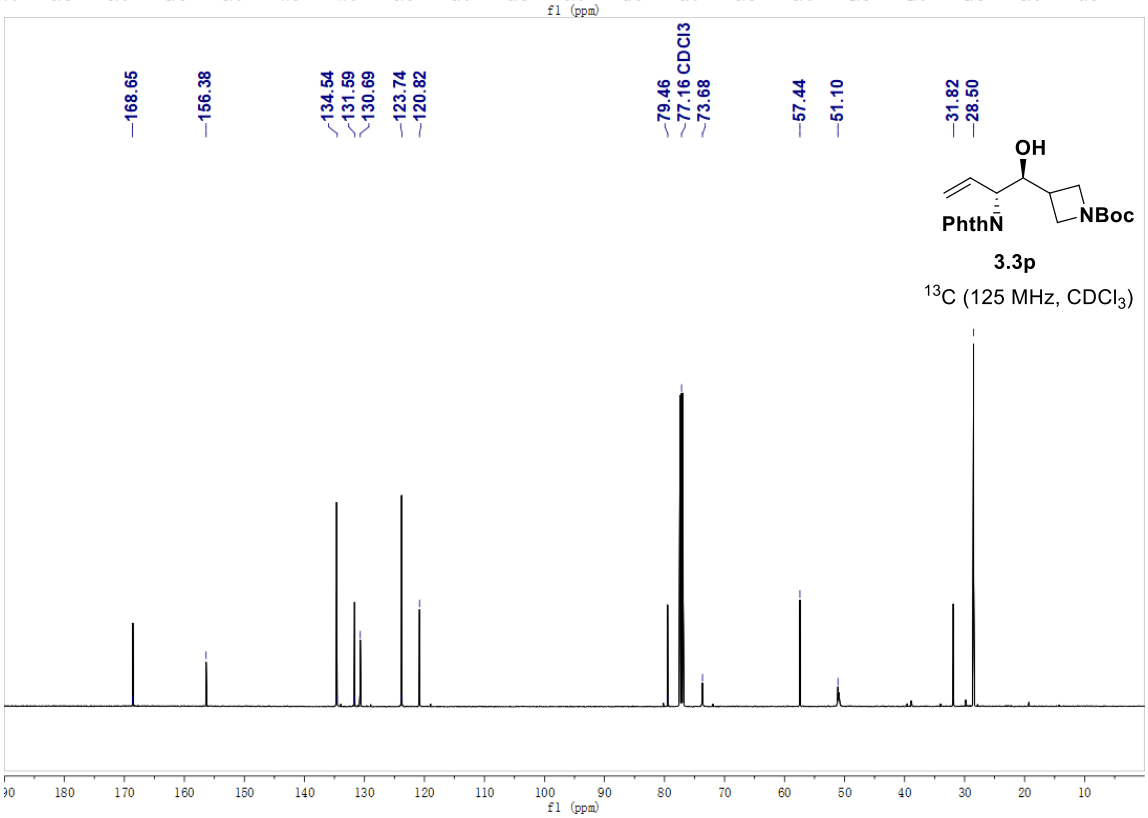
FTIR (neat): 3362, 2360, 2341, 1706, 1275, 1260, 764, 750.

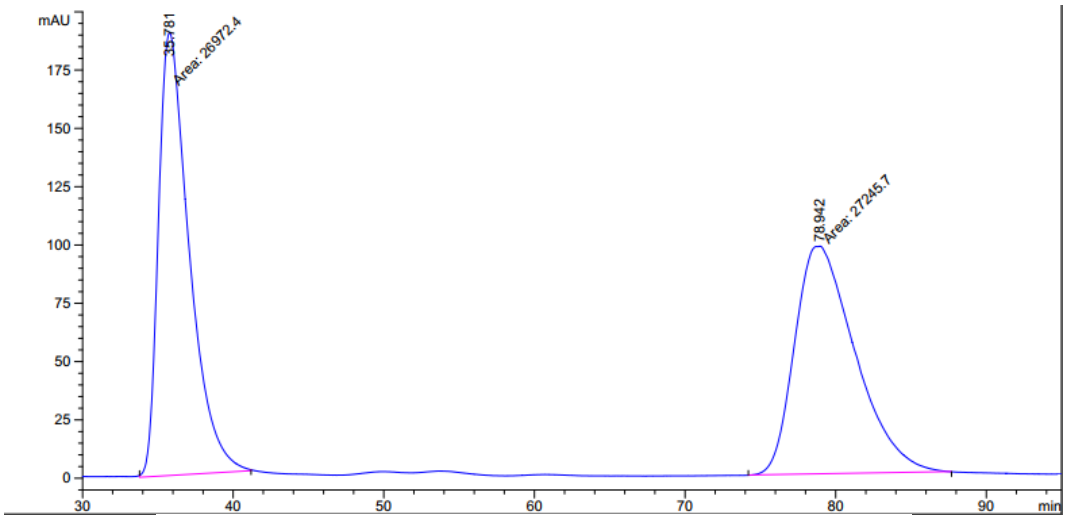
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 97%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +27.7° (c = 0.64, $CHCl_3$).

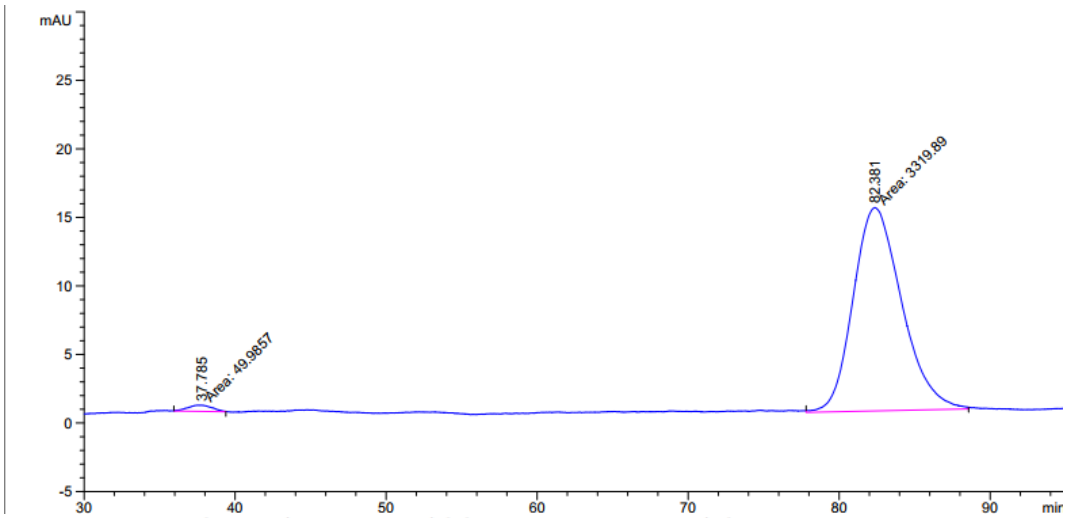
MP [90 – 93] °C


OH
PhthN
NBoc
3.3p
1H (500 MHz, CDCl3)
2.04
2.08
1.00
2.06
1.00
1.03
3.32
1.12
1.01
9.98
f1 (ppm)


168.65
156.38
134.54
131.59
130.69
123.74
120.82
79.46
77.16 CDCl3
73.68
57.44
51.10
31.82
28.50
OH
PhthN
NBoc
3.3p
13C (125 MHz, CDCl3)
f1 (ppm)

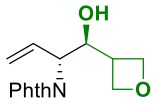


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.781	MM	2.3684	2.69724e4	189.80540	49.7479
2	78.942	MM	4.6552	2.72457e4	97.54673	50.2521



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.785	MM	1.8635	49.98568	4.47063e-1	1.4833
2	82.381	MM	3.7299	3319.89307	14.83440	98.5167

2-((1*S*,2*R*)-1-hydroxy-1-(oxetan-3-yl)but-3-en-2-yl)isoindoline-1,3-dione (3.3q)



3.3q

Alcohol **3.2q** (17.6 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3q** (43.0 mg, 0.16 mmol, >20:1 dr) was obtained as a pale yellow oil in 79% yield.

TLC (SiO_2) R_f = 0.28 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.24 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.32 (d, *J* = 10.7 Hz, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 2H), 4.71 (dd, *J* = 8.1, 6.1 Hz, 1H), 4.56 – 4.53 (m, 2H), 4.36 (dd, *J* = 8.0, 3.5 Hz, 1H), 3.92 (brs, 1H), 3.23 – 3.15 (m, 1H).

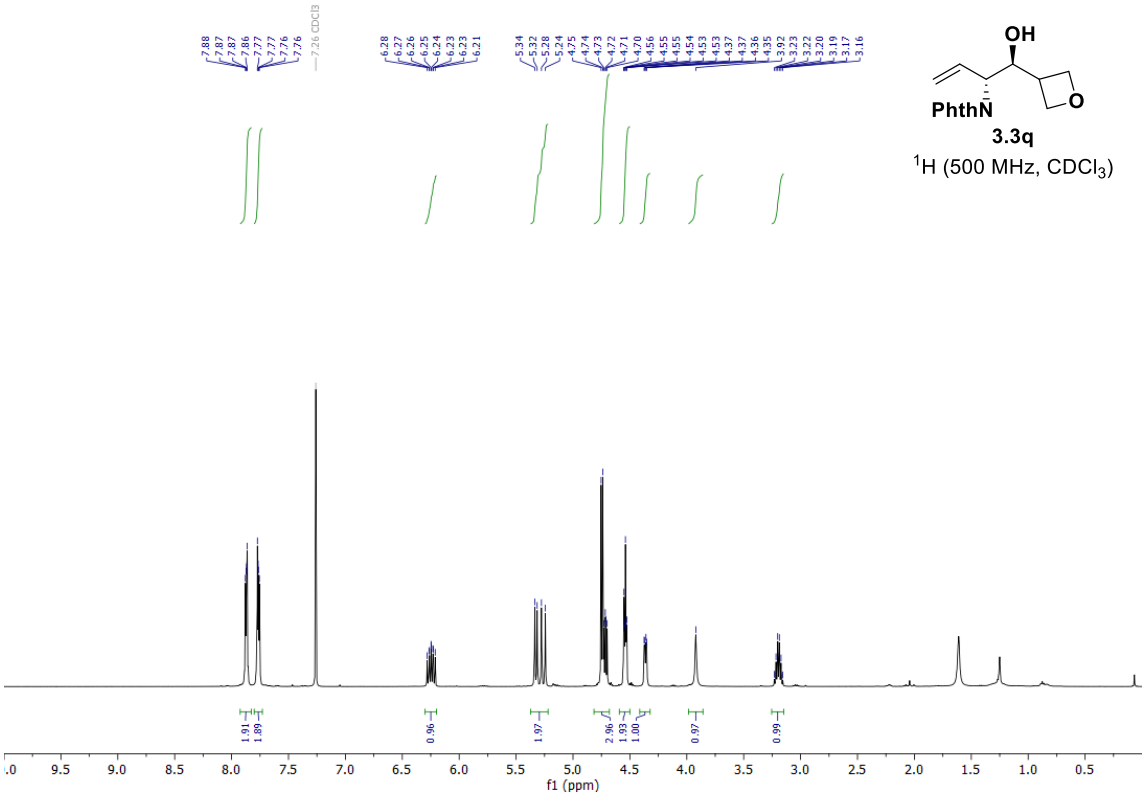
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.7, 131.7, 130.5, 123.9, 120.9, 74.1, 73.9, 73.4, 57.5, 38.2.

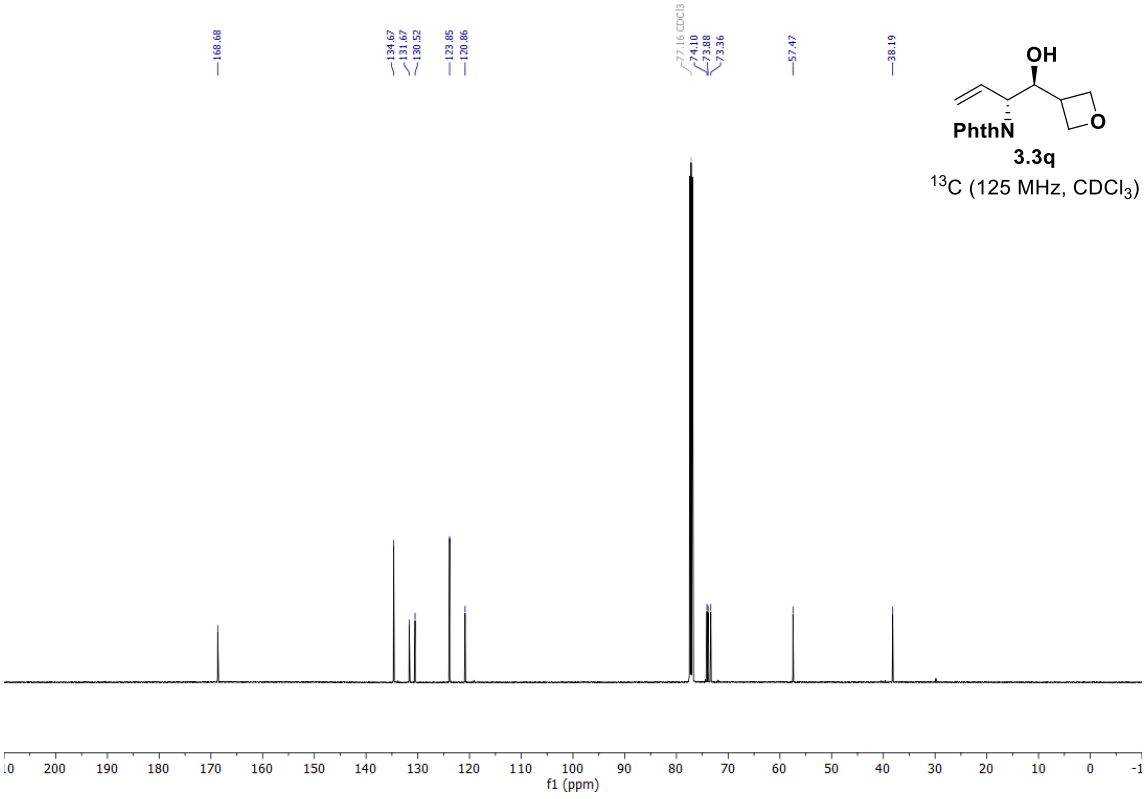
HRMS (Na+, *m/z*) for $C_{15}H_{15}NO_4$: calcd. = 296.0893; found = 296.0901.

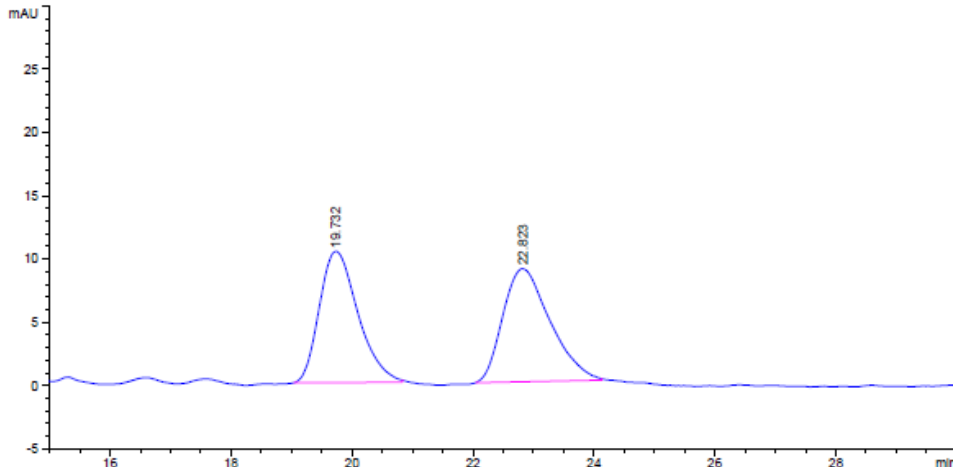
FTIR (neat): 3408, 2959, 2880, 1703, 1380, 973, 718.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 90:10, 1.0 mL/min, 230 nm) ee = 96%.

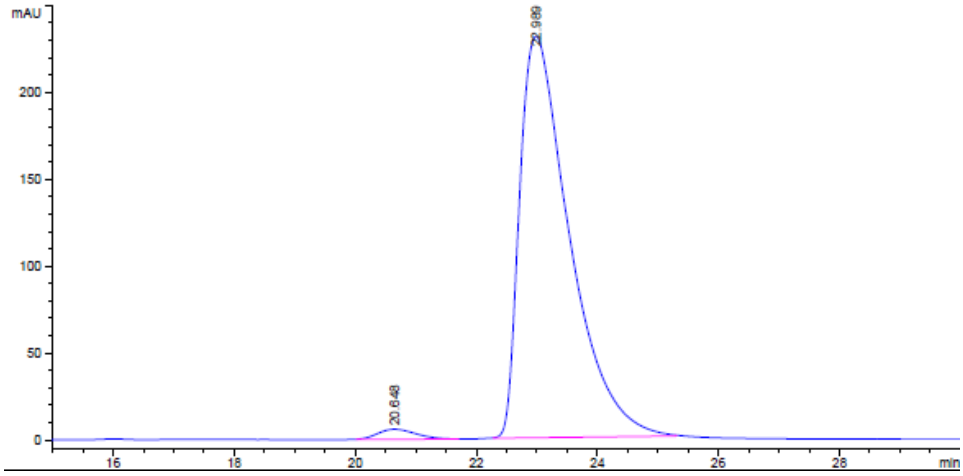
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +38.7° (c = 0.92, $CHCl_3$).


OH
PhthN
O
3.3q
1H (500 MHz, CDCl3)
f1 (ppm)


OH
PhthN
O
3.3q
13C (125 MHz, CDCl3)
f1 (ppm)

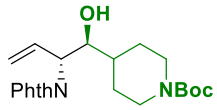


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.732	BB	0.6014	460.60611	10.38528	48.6908
2	22.823	BB	0.7026	485.37595	8.95144	51.3092



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.648	BB	0.5823	251.40669	5.76996	1.8696
2	22.989	BB	0.8464	1.31956e4	231.01495	98.1304

***tert*-butyl 4-((1*S*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)-1-hydroxybut-3-en-1-yl)piperidine-1-carboxylate (3.3r)**



3.3r

Alcohol **3.2r** (40.3 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 25:75 EtOAc:hexanes), the title compound **3.3r** (56.0 mg, 0.14 mmol, >20:1 dr) was obtained as white solid in 70% yield.

TLC (SiO_2) R_f = 0.30 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.33 – 6.23 (m, 1H), 5.34 – 5.23 (m, 2H), 4.89 (dd, *J* = 7.6, 4.2 Hz, 1H), 4.18 – 4.08 (m, 2H), 3.85 (dd, *J* = 6.0, 4.4 Hz, 1H), 3.58 (s, 1H), 2.71 – 2.56 (m, 2H), 1.90 (d, *J* = 13.2 Hz, 1H), 1.67 (d, *J* = 12.7 Hz, 1H), 1.61 – 1.52 (m, 1H), 1.44 (s, 9H), 1.41 – 1.28 (m, 2H)..

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 154.9, 134.6, 131.8, 131.5, 123.8, 120.2, 79.5, 77.2, 75.5, 56.4, 39.0, 29.0, 28.6, 26.9.

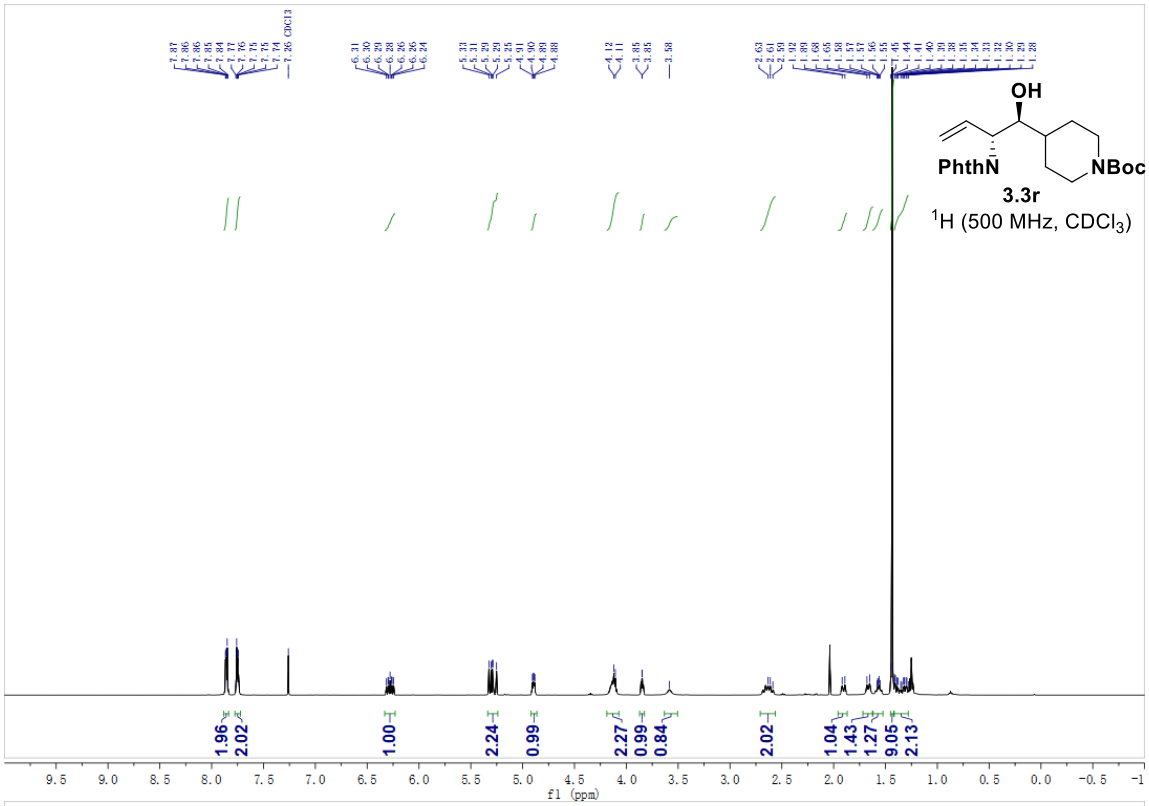
HRMS (K+, *m/z*) for $C_{22}H_{28}N_2O_5$: calcd. = 439.1630; found = 439.1629.

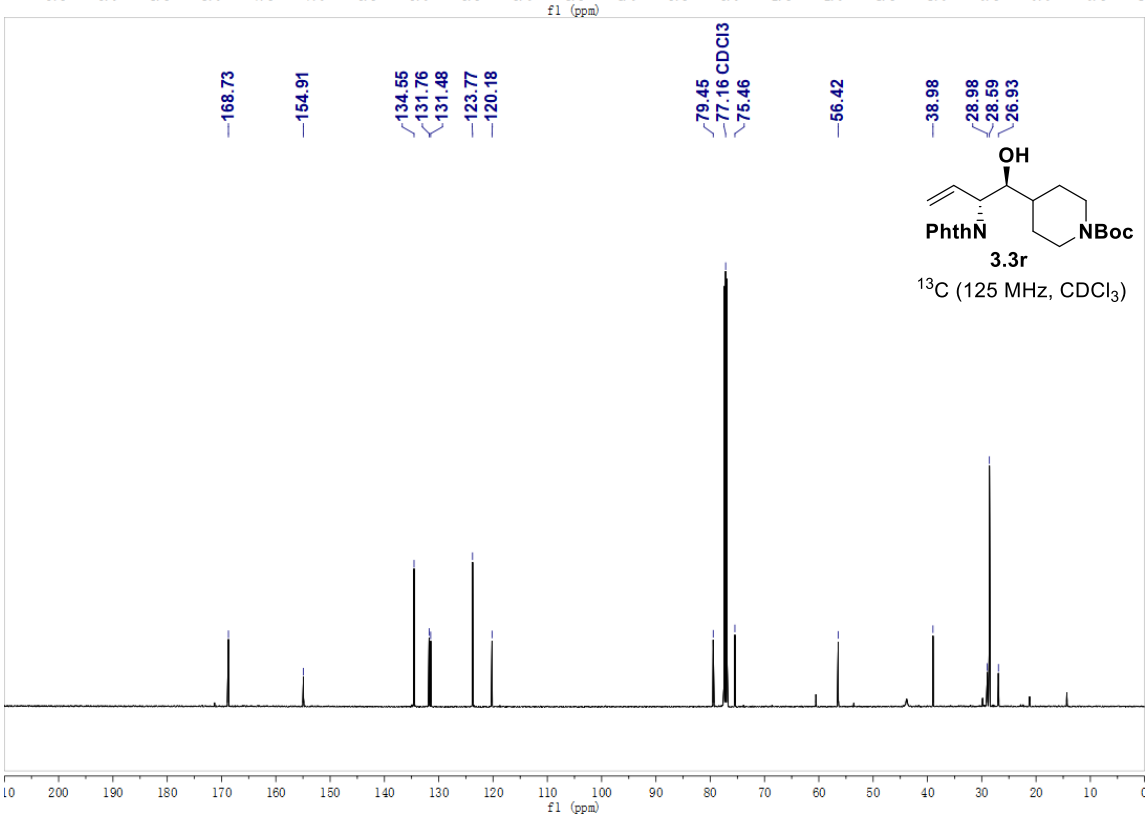
FTIR (neat): 3725, 2989, 2360, 2341, 1707, 1275, 1260, 764, 749, 668.

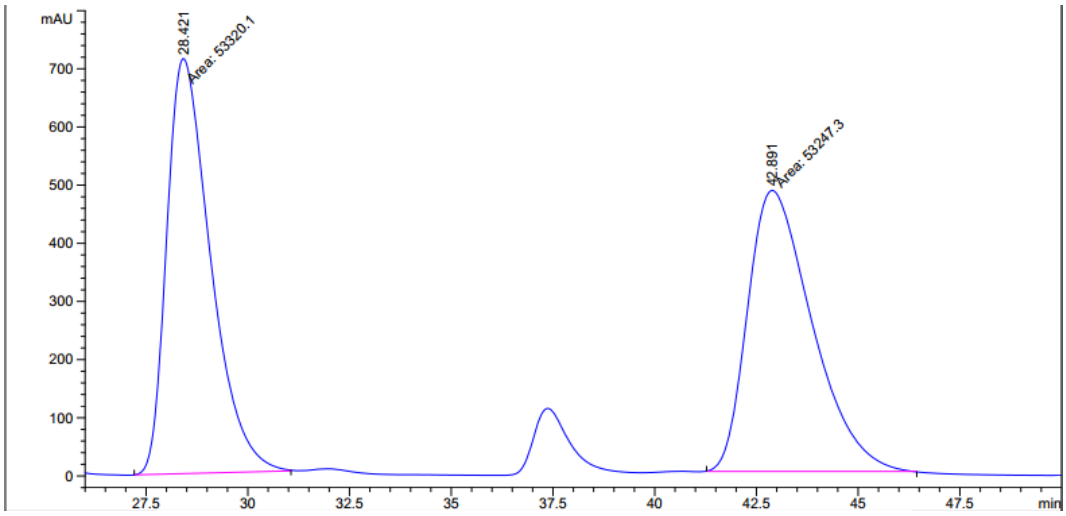
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 93:7, 1.0 mL/min, 230 nm) ee = 93%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +12.6° (c = 0.85, $CHCl_3$).

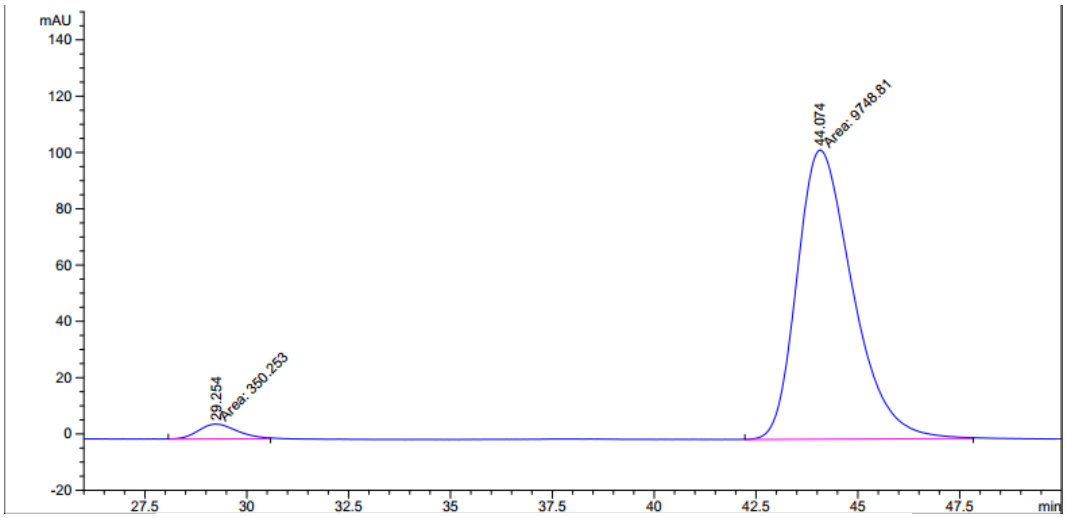
MP [102 – 106] °C


OH
PhthN
NBoc
3.3r
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


OH
PhthN
NBoc
3.3r
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

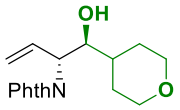


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.421	MM	1.2455	5.33201e4	713.50885	50.0341
2	42.891	MM	1.8368	5.32473e4	483.16492	49.9659



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.254	MM	1.1063	350.25256	5.27671	3.4682
2	44.074	MM	1.5813	9748.81250	102.74837	96.5318

2-((1*S*,2*R*)-1-hydroxy-1-(tetrahydro-2H-pyran-4-yl)but-3-en-2-yl)isoindoline-1,3-dione (3.3s)



3.3s

Alcohol **3.2s** (23.2 mg, 0.2 mmol) was subjected to standard reaction conditions with 7.5 mol% catalyst (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3s** (47.6 mg, 0.158 mmol, >20:1 dr) was obtained as colorless oil in 79% yield.

TLC (SiO_2) R_f = 0.24 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.3, 3.0 Hz, 2H), 6.28 (ddd, *J* = 17.6, 10.2, 7.7 Hz, 1H), 5.29 (dd, *J* = 26.4, 13.7 Hz, 2H), 4.90 (dd, *J* = 7.4, 3.8 Hz, 1H), 3.99 (d, *J* = 11.8 Hz, 2H), 3.82 (dd, *J* = 6.3, 4.0 Hz, 1H), 3.71 (s, 1H), 3.40 – 3.28 (m, 2H), 1.85 (d, *J* = 13.3 Hz, 1H), 1.72 – 1.43 (m, 4H).

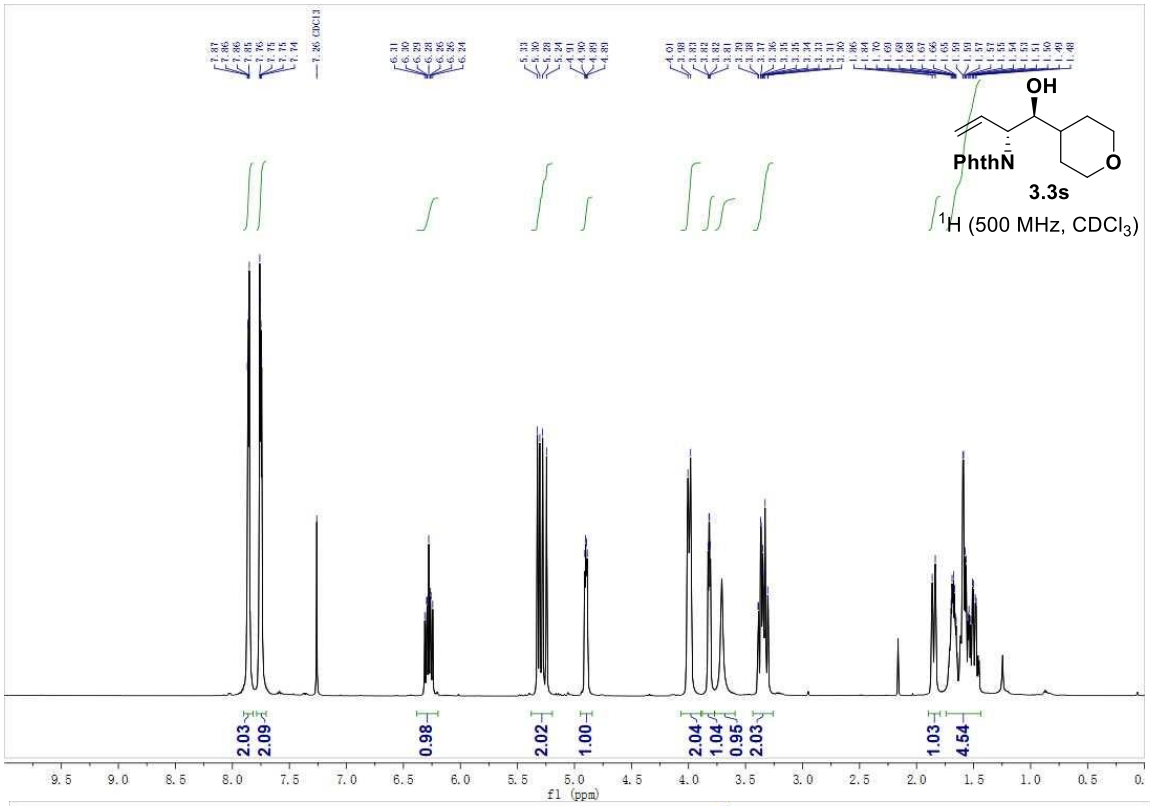
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.6, 131.8, 131.5, 123.8, 120.1, 77.2, 75. 8, 68.1, 67.7, 56.2, 37.9, 29.7, 28.0.

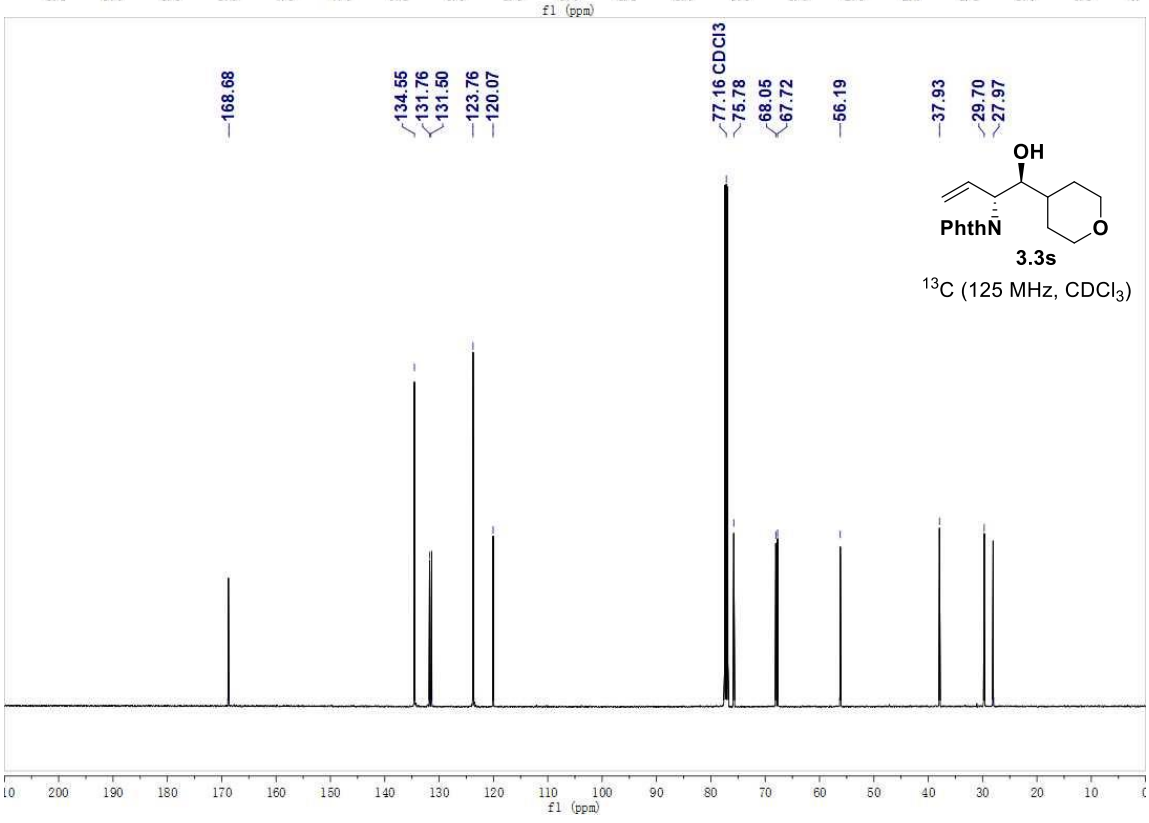
HRMS (H+, *m/z*) for $C_{17}H_{19}NO_4$: calcd. = 302.1387; found = 302.1392.

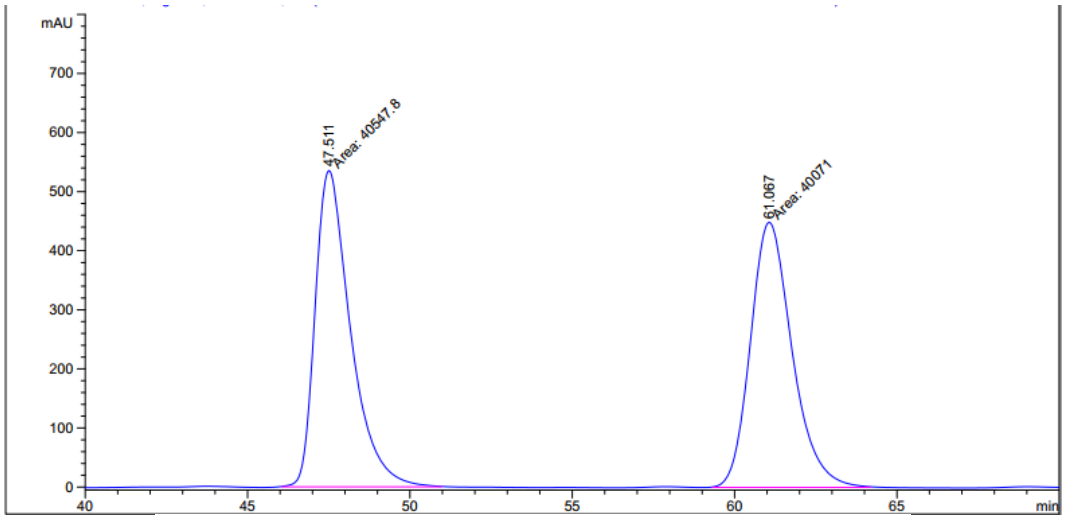
FTIR (neat): 2987, 2360, 2341, 1705, 1383, 1266, 1079, 731.

HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 94%.

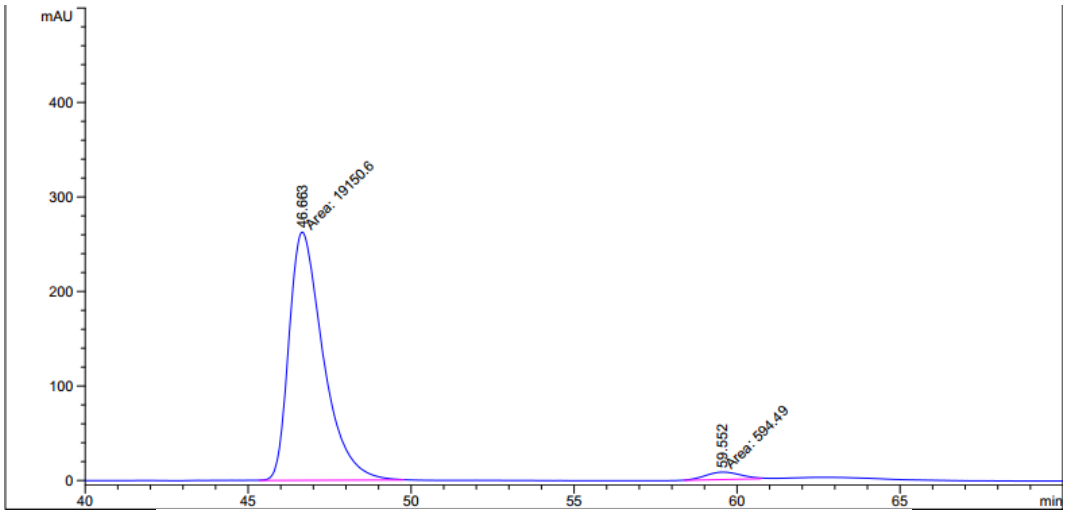
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +42.7° (c = 0.70, $CHCl_3$).


OH
PhthN
O
3.3s
^{1}H (500 MHz, $CDCl_3$)
2.03
2.09
0.98
2.02
1.00
2.04
1.04
0.95
2.03
1.03
4.54
f1 (ppm)


168.68
134.55
131.76
131.50
123.76
120.07
77.16 CDCl3
75.78
68.05
67.72
56.19
37.93
29.70
27.97
OH
PhthN
O
3.3s
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

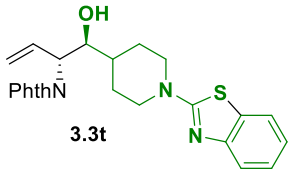


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.511	MM	1.2626	4.05478e4	535.22595	50.2957
2	61.067	MM	1.4888	4.00710e4	448.58865	49.7043



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.663	MM	1.2153	1.91506e4	262.63974	96.9892
2	59.552	MM	1.2566	594.48975	7.88482	3.0108

2-((1*S*,2*R*)-1-(1-(benzo[*d*]thiazol-2-yl)piperidin-4-yl)-1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione (3.3t)



3.3t

Alcohol **3.2t** (49.7 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3t** (58.0 mg, 0.134 mmol, >20:1 dr) was obtained as a light yellow solid in 67% yield.

TLC (SiO_2) R_f = 0.30 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.56 (dd, *J* = 17.4, 7.9 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.30 (ddd, *J* = 17.8, 10.3, 7.8 Hz, 1H), 5.33 (dd, *J* = 19.2, 13.7 Hz, 2H), 4.92 (dd, *J* = 7.6, 4.2 Hz, 1H), 4.24 (d, *J* = 12.4 Hz, 1H), 4.14 (dd, *J* = 9.7, 7.3 Hz, 1H), 3.90 (t, *J* = 6.1 Hz, 1H), 3.63 (d, *J* = 2.4 Hz, 1H), 3.15 – 3.03 (m, 2H), 2.09 (d, *J* = 13.2 Hz, 1H), 1.84 (d, *J* = 12.5 Hz, 1H), 1.74 – 1.51 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.6, 131.7, 131.3, 126.1, 123.9, 121.4, 120.8, 120.5, 119.0, 77.2, 75.2, 56.5, 49.1, 48.6, 38.8, 28.5, 26.5.

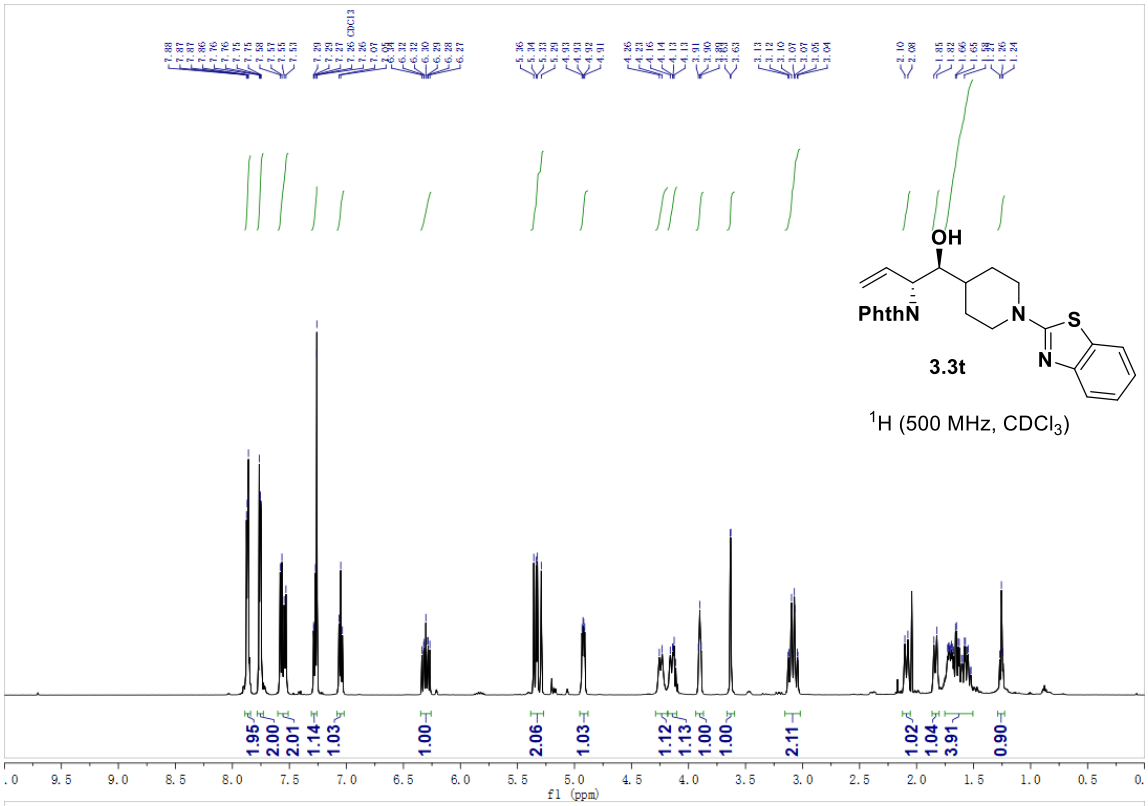
HRMS (H+, *m/z*) for $C_{24}H_{23}N_3O_3S$: calcd. = 434.1533; found = 434.1534.

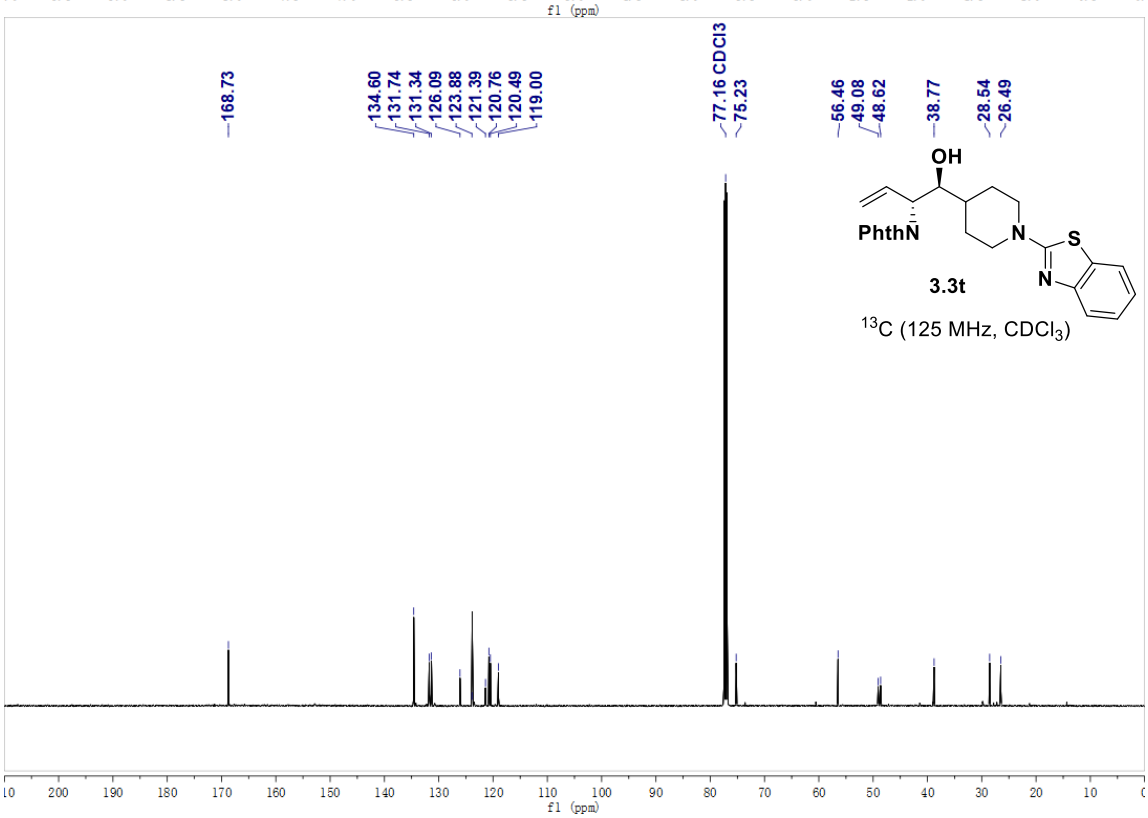
FTIR (neat): 2923, 2360, 2341, 1705, 1356, 1275, 763, 750.

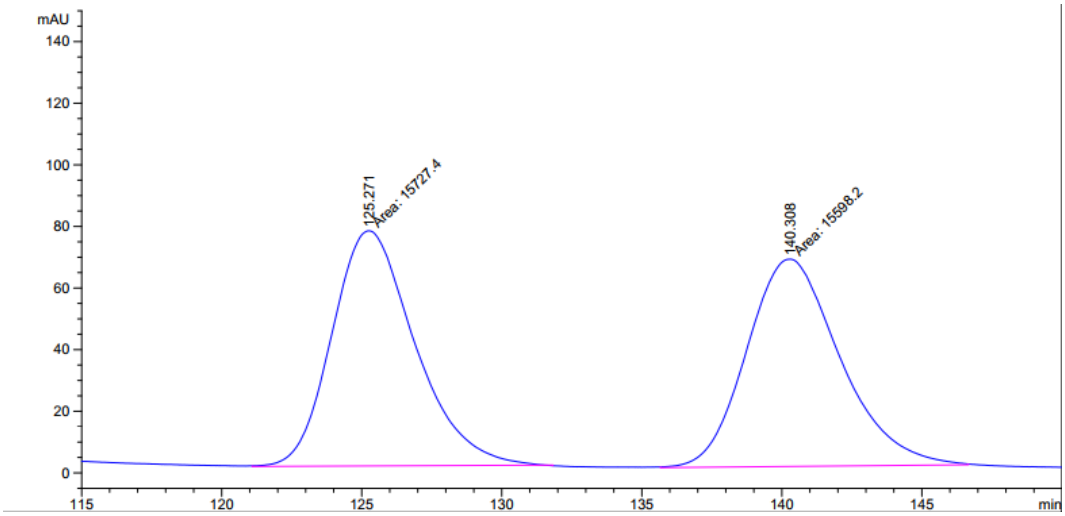
HPLC: (Chiralcel column AD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 94%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +52.0° (c = 0.72, $CHCl_3$).

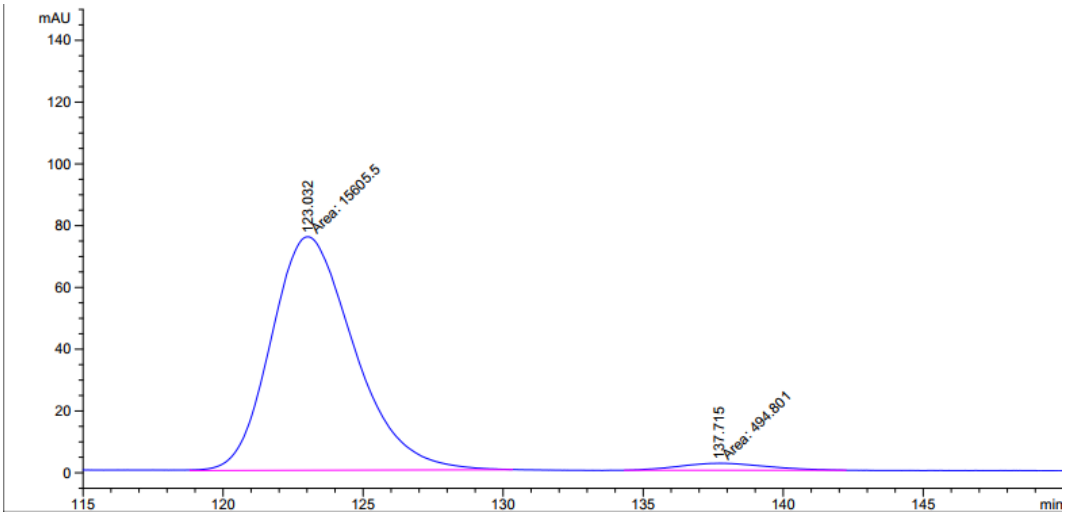
MP [80 – 84] °C


OH
PhthN
N
S
N
3.3t
1H (500 MHz, CDCl3)
1.95
2.00
2.01
1.14
1.03
1.00
2.06
1.03
1.12
1.13
1.00
1.00
2.11
1.02
1.04
3.91
0.90
f1 (ppm)


168.73
134.60
131.74
131.34
126.09
123.88
121.39
120.76
120.49
119.00
77.16 CDCl3
75.23
56.46
49.08
48.62
38.77
28.54
26.49
OH
PhthN
N
S
N
3.3t
13C (125 MHz, CDCl3)
f1 (ppm)

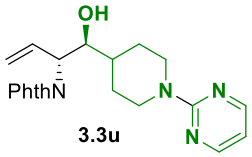


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	125.271	MM	3.4347	1.57274e4	76.31709	50.2062
2	140.308	MM	3.8646	1.55982e4	67.26893	49.7938



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	123.032	MM	3.4409	1.56055e4	75.58755	96.9268
2	137.715	MM	3.6153	494.80118	2.28103	3.0732

2-((1*S*,2*R*)-1-hydroxy-1-(1-(pyrimidin-2-yl)piperidin-4-yl)but-3-en-2-yl)isoindoline-1,3-dione (3.3u)



Alcohol **3.2u** (38.6 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) using 7.5 mol% of (*R*)-Ir-**VI**. Upon flash column chromatography (SiO_2, 30:70 EtOAc:hexanes), the title compound **3.3u** (54.5 mg, 0.144 mmol, >20:1 dr) was obtained as a pale yellow oil in 72% yield.

TLC (SiO_2) R_f = 0.2 (30:70 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 4.7 Hz, 2H), 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.43 (t, *J* = 4.7 Hz, 1H), 6.36 – 6.24 (m, 1H), 5.31 (dd, *J* = 20.9, 13.7 Hz, 2H), 4.94 (dd, *J* = 7.5, 4.1 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 2H), 3.90 – 3.83 (m, 1H), 3.62 (d, *J* = 2.4 Hz, 1H), 2.82 (dtd, *J* = 15.5, 13.1, 2.5 Hz, 2H), 2.03 (d, *J* = 13.1 Hz, 1H), 1.79 (d, *J* = 12.8 Hz, 1H), 1.72 (tt, *J* = 6.8, 4.2 Hz, 1H), 1.44 (dddd, *J* = 29.0, 25.0, 12.6, 4.3 Hz, 2H)..

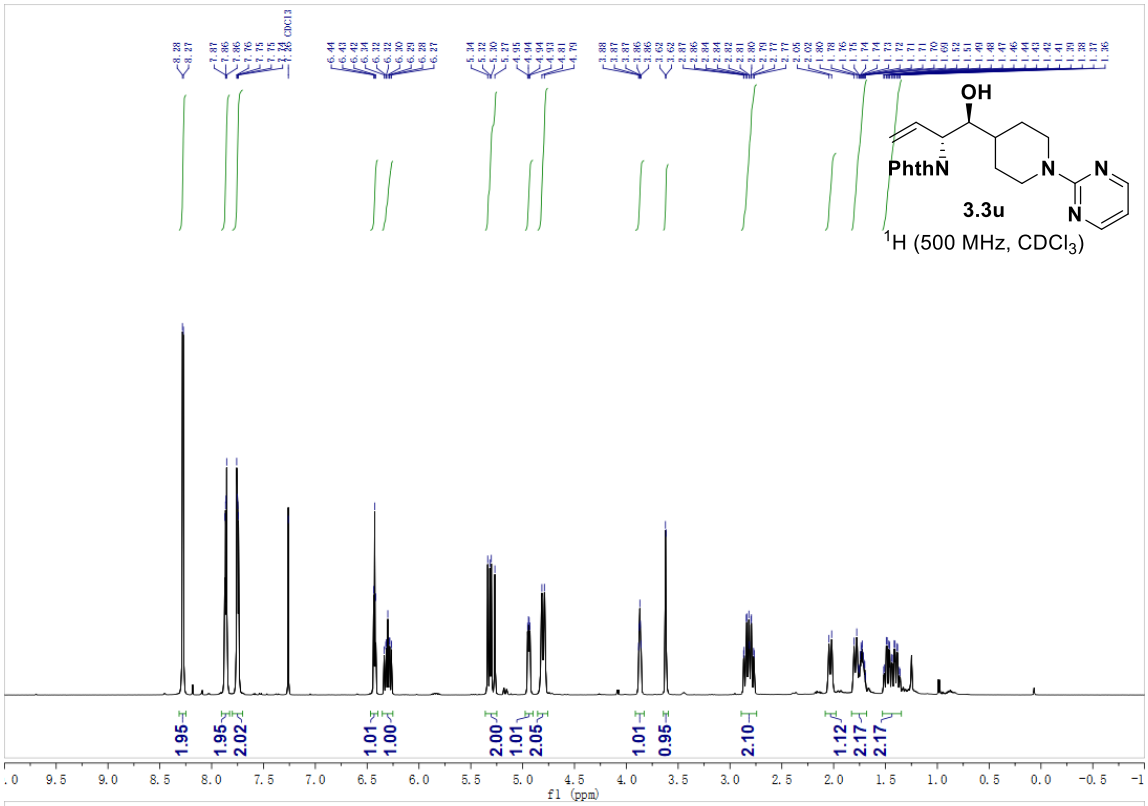
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 157.8, 134.5, 131.8, 131.5, 123.8, 120.1, 77.2, 75.6, 56.5, 44.0, 43.9, 39.3, 28.9, 26.9.

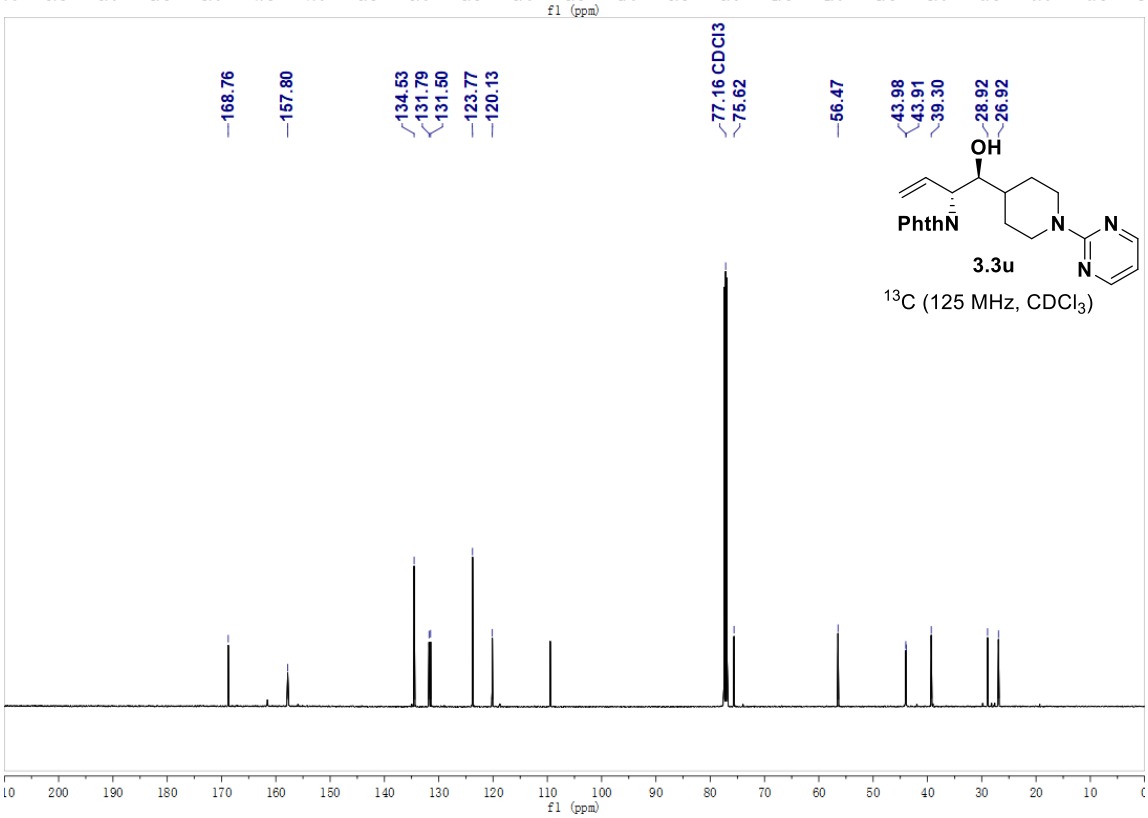
HRMS (Na+, *m/z*) for $C_{21}H_{22}N_4O_3$: calcd. = 401.1584; found = 401.1594.

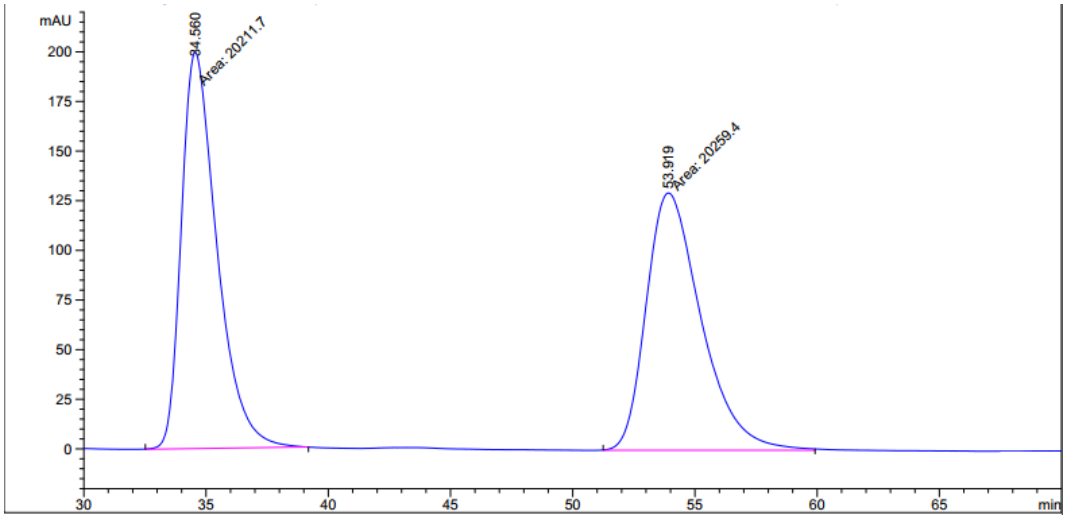
FTIR (neat): 3356, 1707, 1587, 1264, 1073, 976, 733, 703.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 95%.

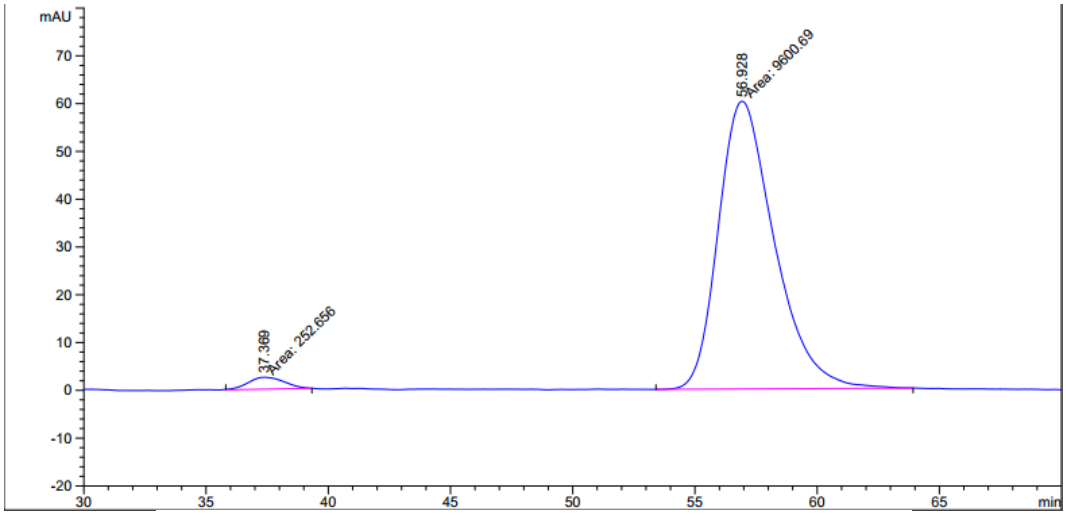
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +35.5° (c = 0.77, $CHCl_3$).


OH
PhthN
N
N
N
3.3u
1H (500 MHz, CDCl3)
1.95
1.95
2.02
1.01
1.00
2.00
1.01
2.05
1.01
0.95
2.10
1.12
2.17
2.17
f1 (ppm)


168.76
157.80
134.53
131.79
131.50
123.77
120.13
77.16 CDCl3
75.62
56.47
43.98
43.91
39.30
28.92
26.92
OH
PhthN
N
N
N
3.3u
13C (125 MHz, CDCl3)
f1 (ppm)

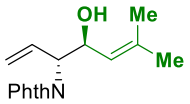


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.560	MM	1.6868	2.02117e4	199.70801	49.9411
2	53.919	MM	2.6059	2.02594e4	129.57588	50.0589



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.369	MM	1.7079	252.65567	2.46558	2.5642
2	56.928	MM	2.6581	9600.69336	60.19681	97.4358

2-((3*R*,4*S*)-4-hydroxy-6-methylhepta-1,5-dien-3-yl)isoindoline-1,3-dione (3.3v)



3.3v

Alcohol **3.2v** (17.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3v** (38.0 mg, 0.14 mmol, >20:1 dr) was obtained as a light yellow solid in 70% yield.

TLC (SiO_2) R_f = 0.2 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.38 (ddd, *J* = 17.2, 10.4, 7.8 Hz, 1H), 5.32 (ddd, *J* = 15.1, 10.6, 3.6 Hz, 2H), 5.22 – 5.13 (m, 1H), 4.91 (dd, *J* = 8.9, 6.8 Hz, 1H), 4.67 (dd, *J* = 7.7, 6.8 Hz, 1H), 1.61 (dd, *J* = 11.3, 0.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 138.5, 134.3, 132.1, 131.8, 124.0, 123.6, 120.4, 77.2, 68.8, 59.4, 25.9, 18.5.

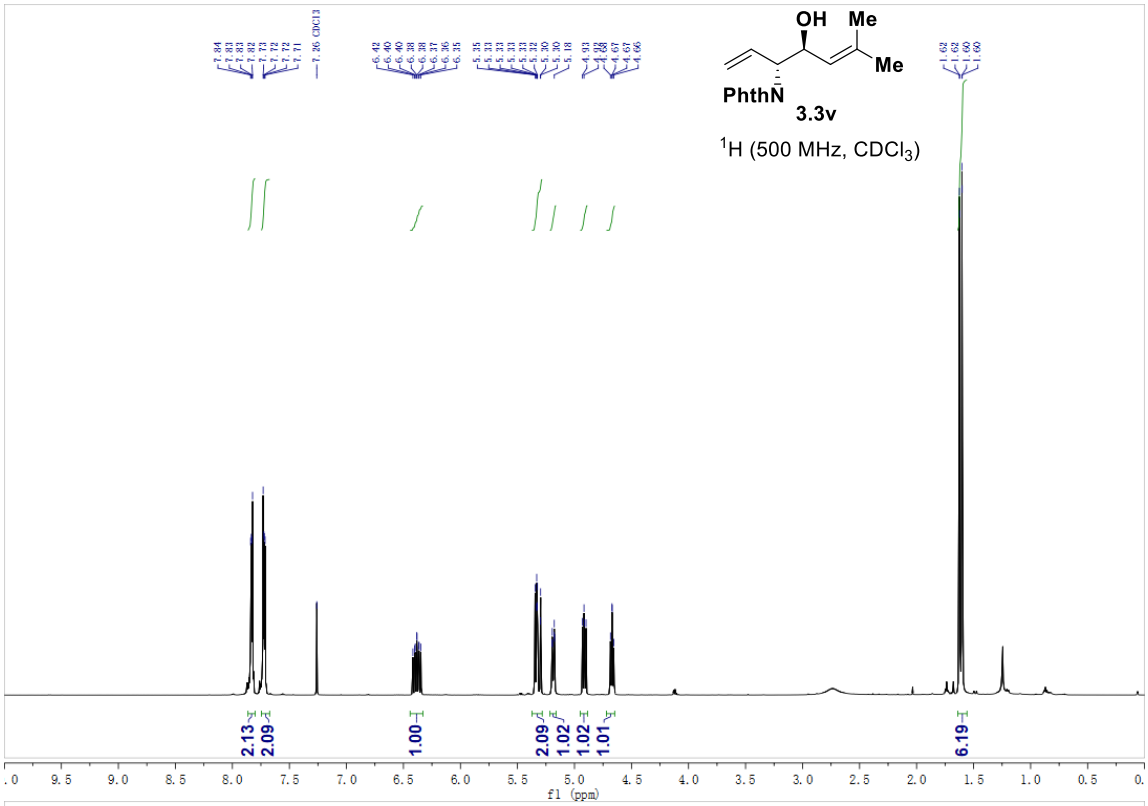
HRMS (Na+, *m/z*) for $C_{16}H_{17}NO_3$: calcd. = 294.1101; found = 294.1108.

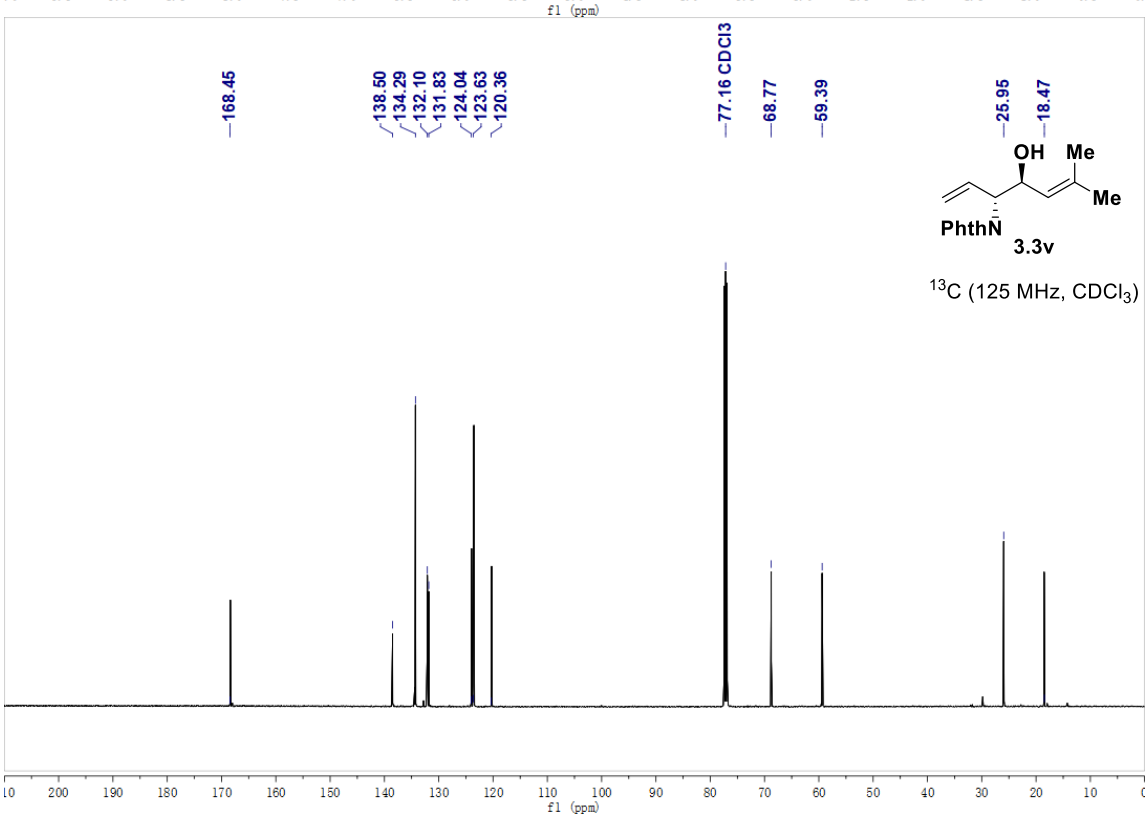
FTIR (neat): 2988, 2358, 2340, 1769, 1703, 764, 733.

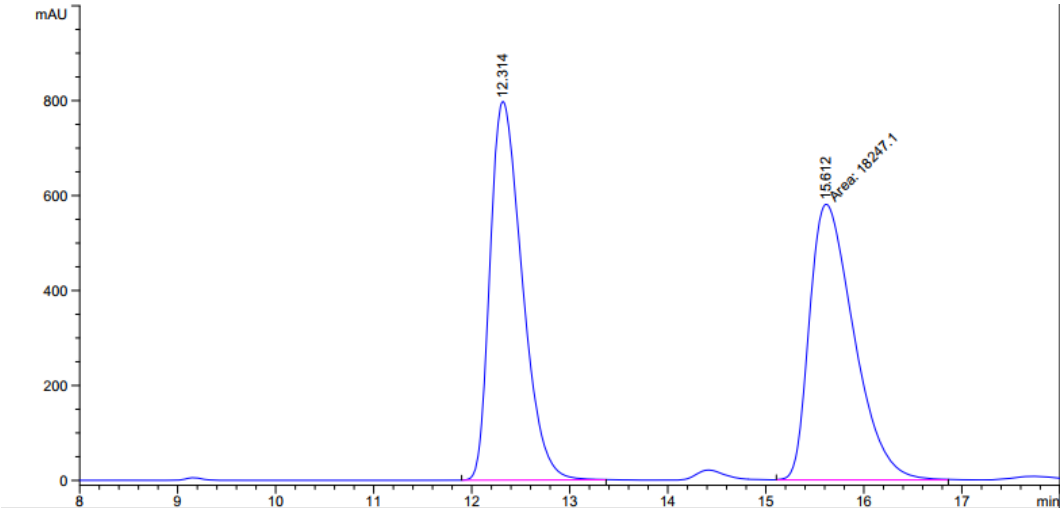
HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 86%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +46.3° (c = 0.62 $CHCl_3$).

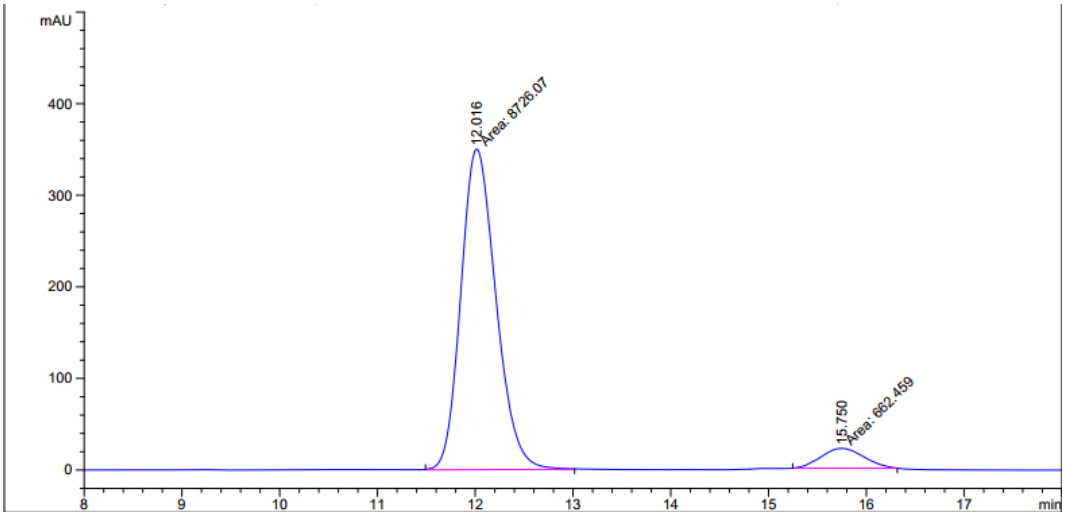
MP [78-82] °C


OH
Me
Me
PhthN
3.3v
^{1}H (500 MHz, $CDCl_3$)
2.13
2.09
1.00
2.09
1.02
1.02
1.01
6.19
f1 (ppm)


168.45
138.50
134.29
132.10
131.83
124.04
123.63
120.36
77.16 CDCl3
68.77
59.39
25.95
18.47
OH
Me
Me
PhthN
3.3v
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

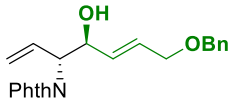


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.314	BB	0.3551	1.81240e4	797.47308	49.8308
2	15.612	MM	0.5239	1.82471e4	580.51849	50.1692



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.016	MM	0.4152	8726.07422	350.31497	92.9440
2	15.750	MM	0.5071	662.45856	21.77350	7.0560

2-((3*R*,4*S*,*E*)-7-(benzyloxy)-4-hydroxyhepta-1,5-dien-3-yl)isoindoline-1,3-dione (3.3w)



3.3w

Alcohol **3.2w** (35.6 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3w** (50 mg, 0.138 mmol, >20:1 dr) was obtained as a light yellow oil in 69% yield.

TLC (SiO_2) R_f = 0.30 (30:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.27 – 7.24 (m, 2H), 6.36 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.95 (dd, *J* = 13.3, 7.7 Hz, 1H), 5.81 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.41 – 5.31 (m, 2H), 4.79 (dt, *J* = 23.1, 6.2 Hz, 2H), 4.40 (s, 2H), 4.00 (qd, *J* = 13.0, 5.6 Hz, 2H), 3.28 (s, 1H).

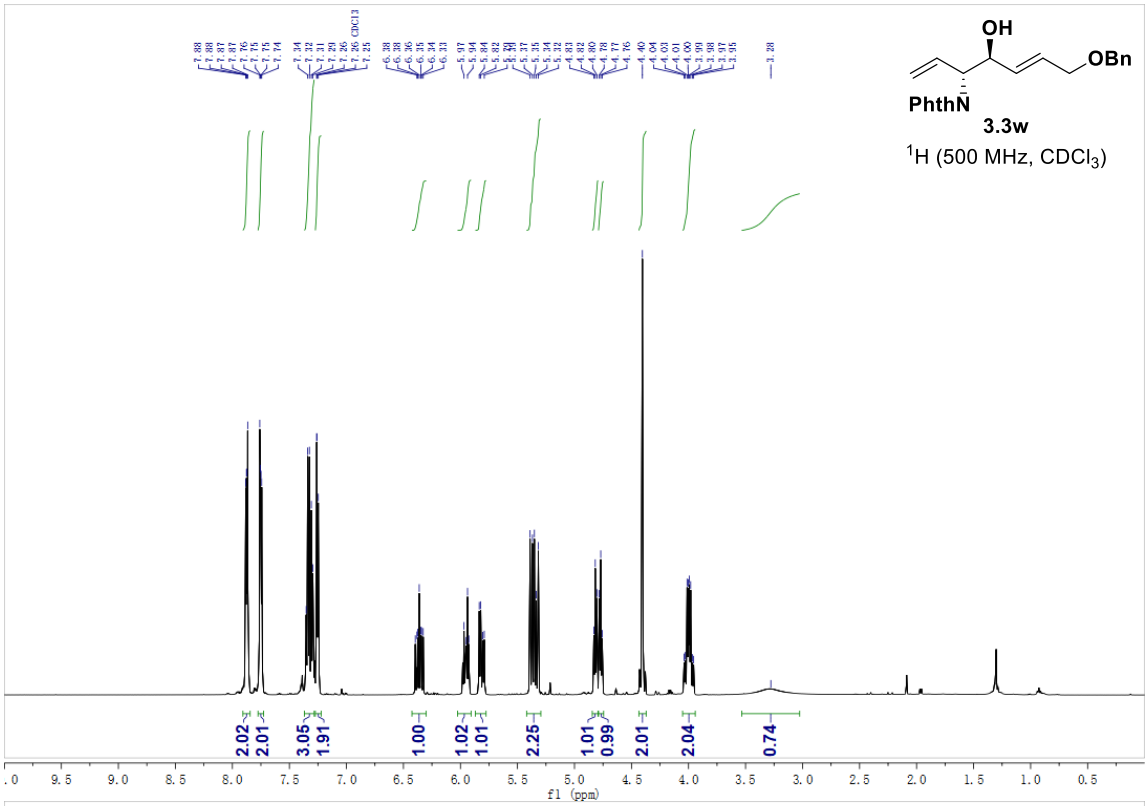
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.4, 138.2, 134.4, 131.7, 131.5, 131.4, 130.5, 128.4, 127.7, 127.7, 123.6, 120.1, 77.2, 72.3, 71.9, 69.8, 59.0.

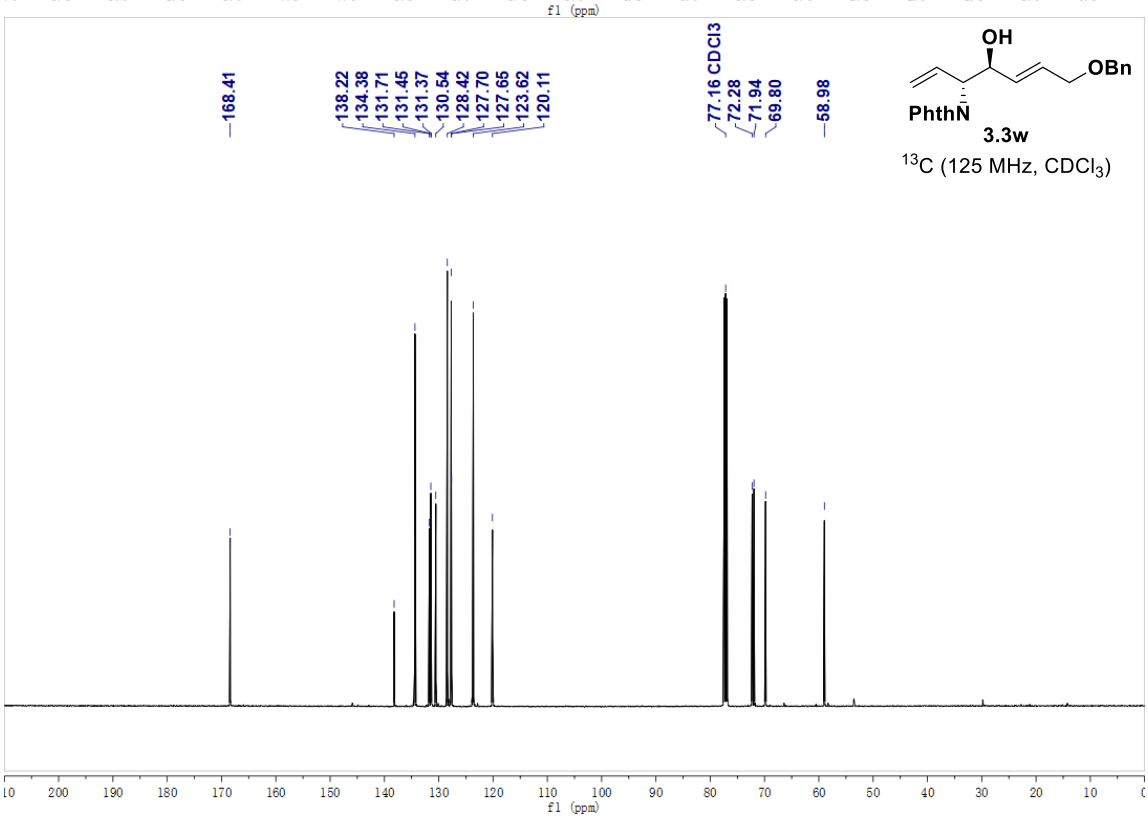
HRMS (Na+, *m/z*) for $C_{22}H_{21}NO_4$: calcd. = 386.1363; found = 386.1361.

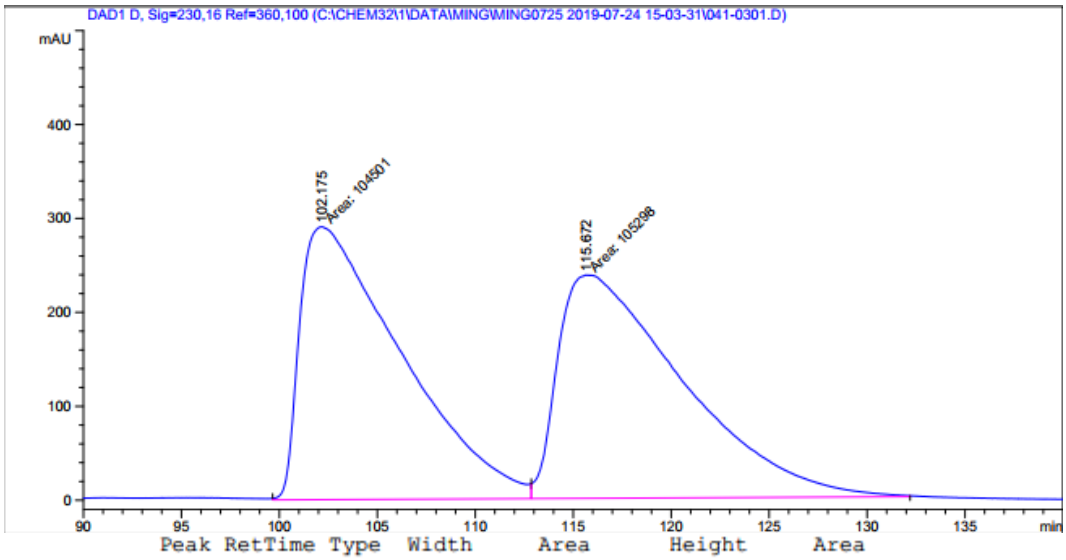
FTIR (neat): 2988, 2358, 2340, 1769, 1703, 1383, 1264, 764.

HPLC: (Chiralcel column OJ-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 86%.

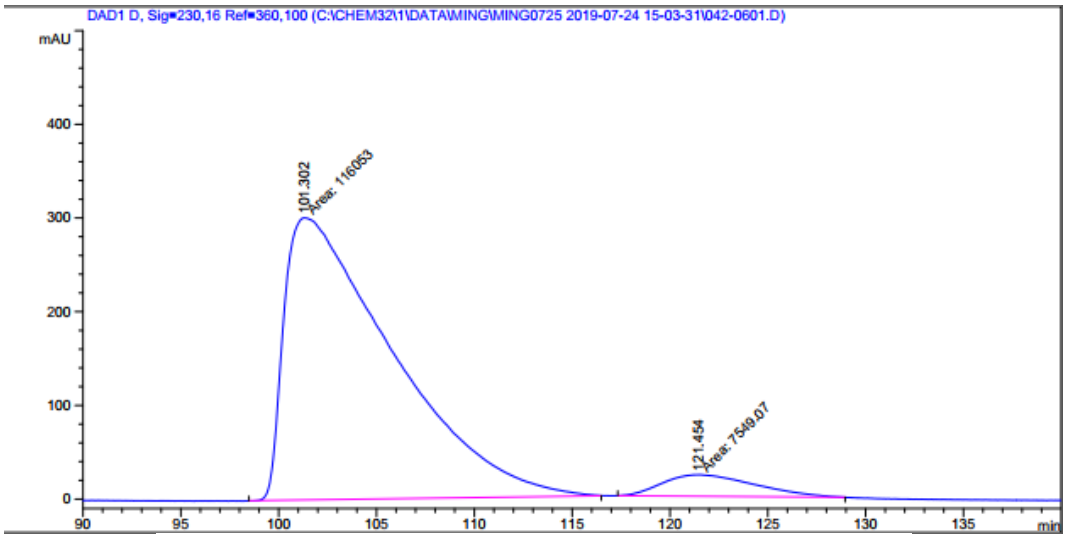
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 75.2° (c = 0.37, $CHCl_3$).


OH
OBn
PhthN
3.3w
1H (500 MHz, CDCl3)
2.02
2.01
3.05
1.91
1.00
1.02
1.01
2.25
1.01
0.99
2.01
2.04
0.74
f1 (ppm)


OH
OBn
PhthN
3.3w
13C (125 MHz, CDCl3)
168.41
138.22
134.38
131.71
131.45
131.37
130.54
128.42
127.70
127.65
123.62
120.11
77.16 CDCl3
72.28
71.94
69.80
58.98
f1 (ppm)

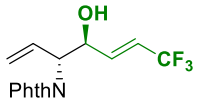


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	102.175	MF	5.9982	1.04501e5	290.36563	49.8101
2	115.672	FM	7.3818	1.05298e5	237.74234	50.1899



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	101.302	MM	6.4237	1.16053e5	301.10715	93.8924
2	121.454	MM	5.4559	7549.06543	23.06065	6.1076

2-((3*R*,4*S*,*E*)-7,7,7-trifluoro-4-hydroxyhepta-1,5-dien-3-yl)isoindoline-1,3-dione (3.3x)



3.3x

Alcohol **3.2x** (25.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) using 7.5 mol% of (*R*)-Ir-**VI**. Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3x** (38.1 mg, 0.12 mmol, >20:1 dr) was obtained as a light yellow solid in 61% yield.

TLC (SiO_2) R_f = 0.40 (20:80 EtOAc:hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.41 (ddq, *J* = 15.6, 4.3, 2.2 Hz, 1H), 6.17 (ddd, *J* = 17.0, 10.4, 6.7 Hz, 1H), 6.11 – 6.04 (m, 1H), 5.35 (d, *J* = 10.7 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 4.86 – 4.84 (m, 1H), 4.78 – 4.76 (m, 1H), 4.15 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 138.0 (q, *J* = 6.3 Hz), 134.8, 131.6, 129.6, 124.0, 123.0 (q, *J* = 270 Hz), 120.9 (q, *J* = 121 Hz), 120.6, 71.2, 58.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ: -64.4 (dt, J = 6.8, 2.6 Hz).

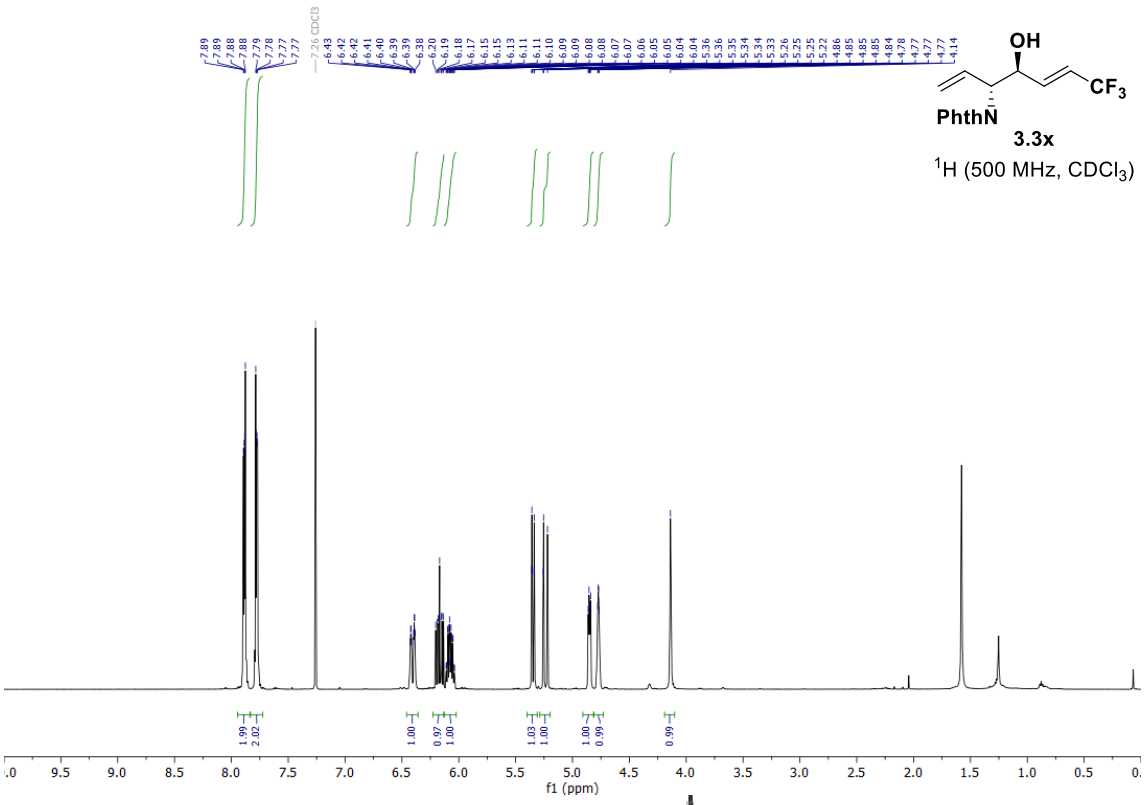
HRMS (Na+, *m/z*) for $C_{15}H_{12}F_3NO_3$: calcd. = 334.0665; found = 334.0661.

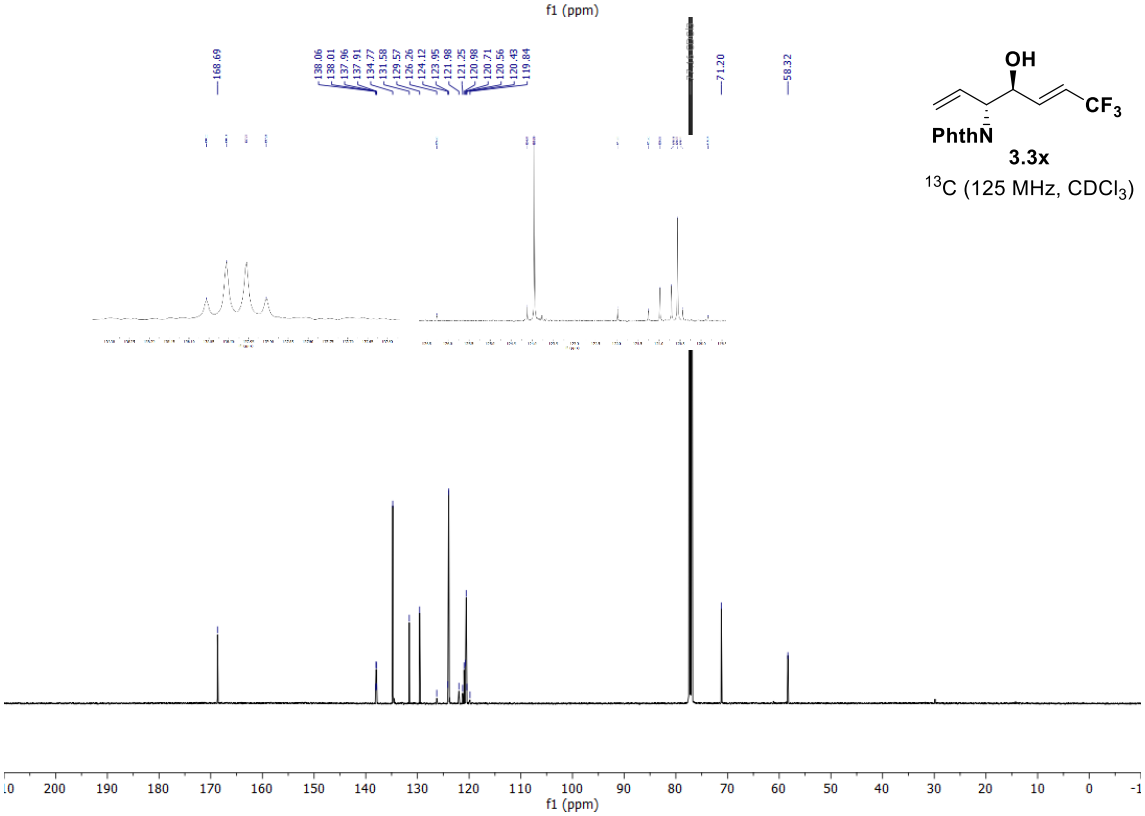
FTIR (neat): 3456, 3333, 2359, 1687, 1330, 1077, 712.

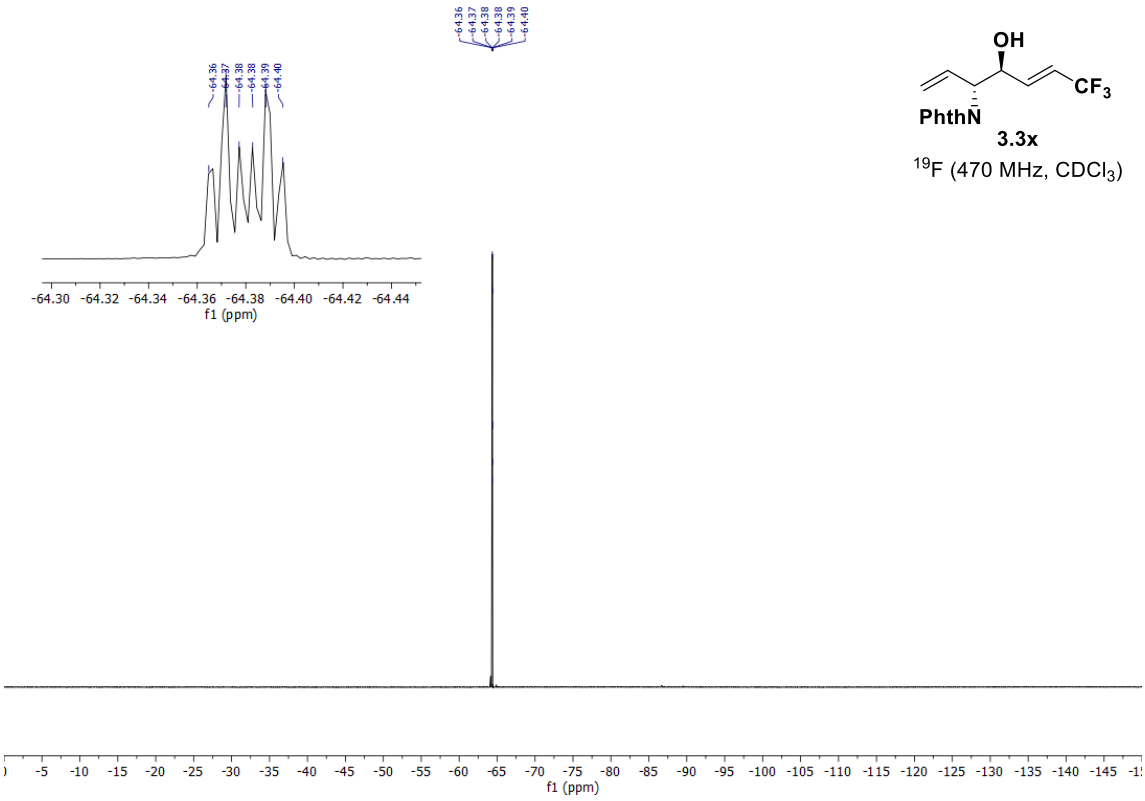
HPLC: (Chiralcel column AS-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 90%.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +38.6° (c = 1.18, $CHCl_3$).

MP [109 – 112] °C

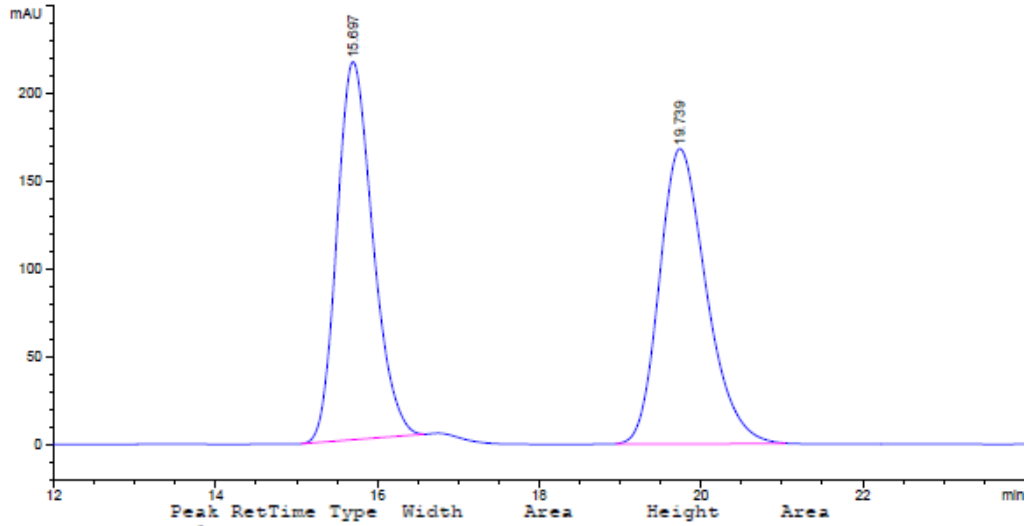

OH
CF3
PhthN
3.3x
1H (500 MHz, CDCl3)
f1 (ppm)


OH
CF3
PhthN
3.3x
13C (125 MHz, CDCl3)
f1 (ppm)

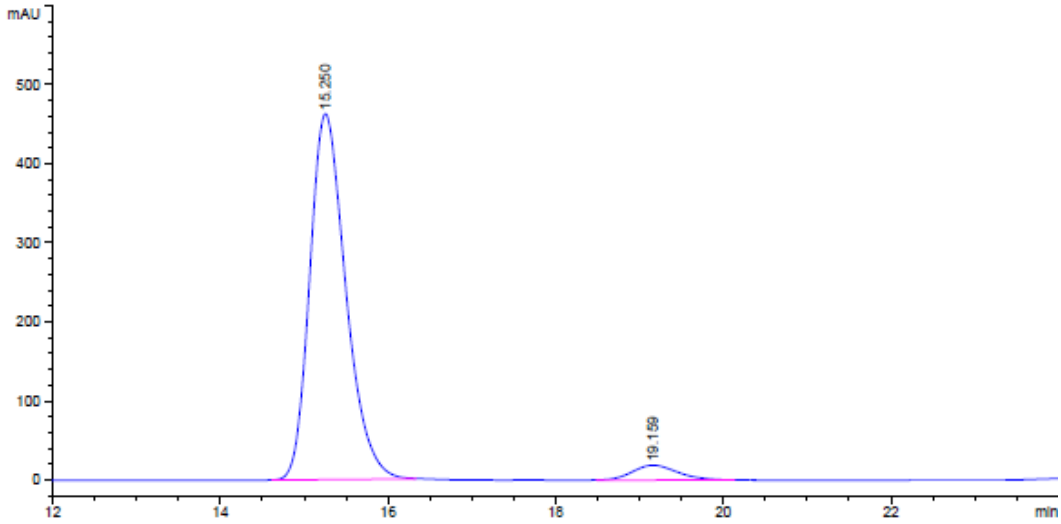


3.3x

^{19}F (470 MHz, $CDCl_3$)

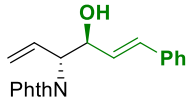


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.697	BB	0.4751	6620.58594	215.07155	49.3982
2	19.739	BB	0.6169	6781.90039	168.01593	50.6018



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.250	BB	0.4587	1.38192e4	462.34772	95.0950
2	19.159	BB	0.5691	712.79950	18.85224	4.9050

2-((3*R*,4*S*,*E*)-4-hydroxy-6-phenylhexa-1,5-dien-3-yl)isoindoline-1,3-dione (3.3y)



3.3y

Alcohol **3.2y** (27 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound **3.3y** (45 mg, 0.14 mmol, >20:1 dr) was obtained as a light yellow oil in 71% yield.

TLC (SiO_2) R_f = 0.35 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.32 – 7.29 (m, 5H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.36 (ddd, *J* = 17.0, 10.4, 6.7 Hz, 1H), 6.20 (dd, *J* = 15.9, 6.2 Hz, 1H), 5.35 (d, *J* = 10.7 Hz, 1H), 5.31 (d, *J* = 17.0 Hz, 1H), 4.89 – 4.84 (m, 2H), 3.34 (s, 1H).

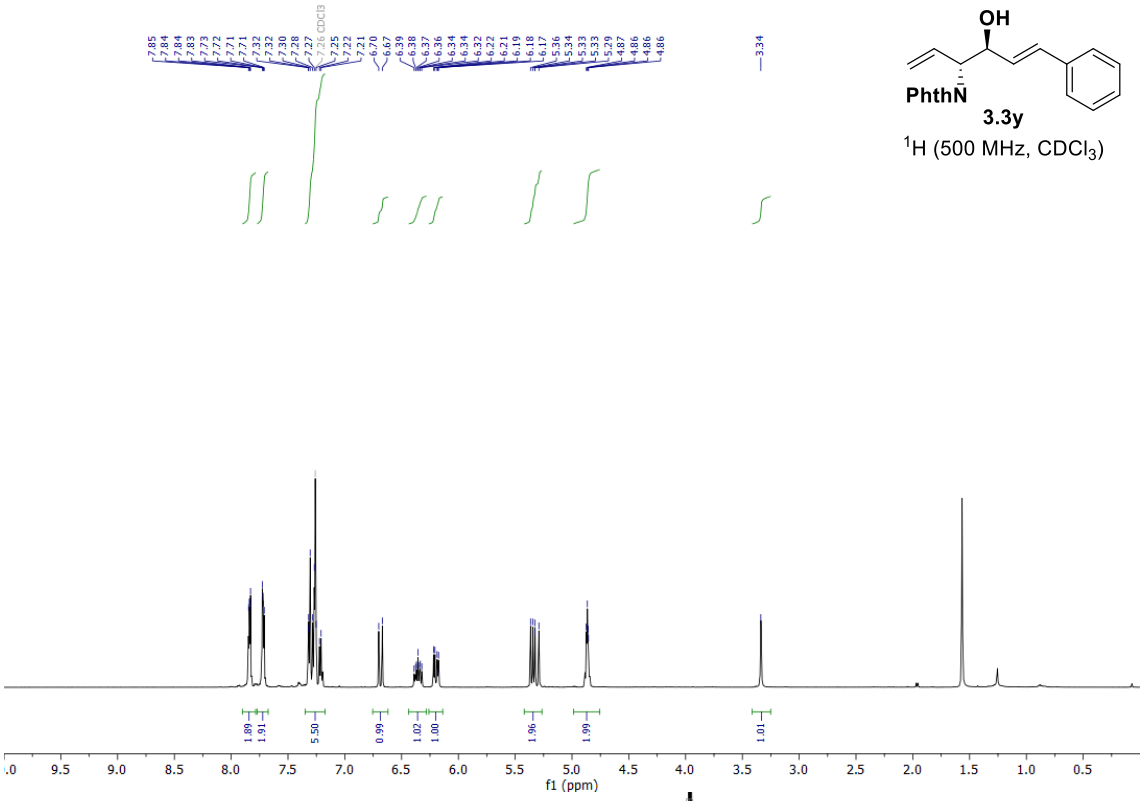
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 136.5, 134.5, 133.2, 131.8, 131.3, 128.7, 128.1, 128.0, 126.8, 123.7, 120.2, 73.1, 59.2.

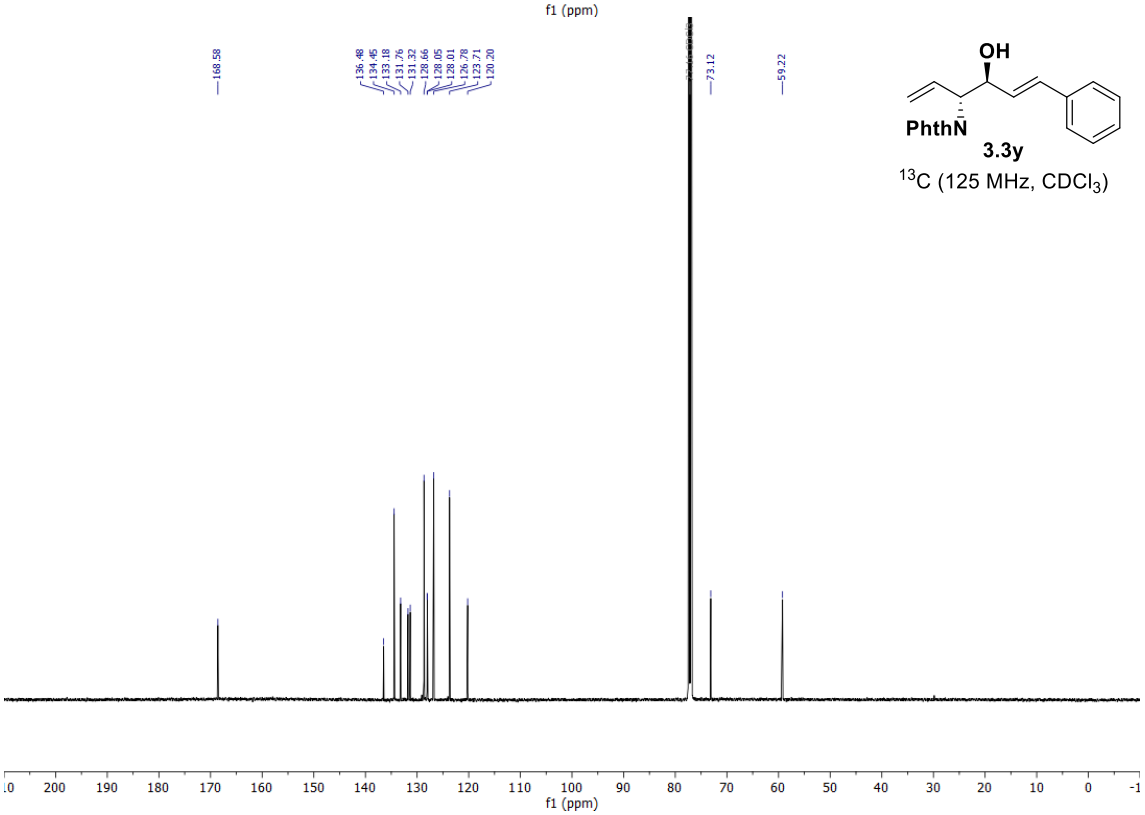
HRMS (Na+, *m/z*) for $C_{20}H_{17}NO_3$: calcd. = 342.1101; found = 342.1106.

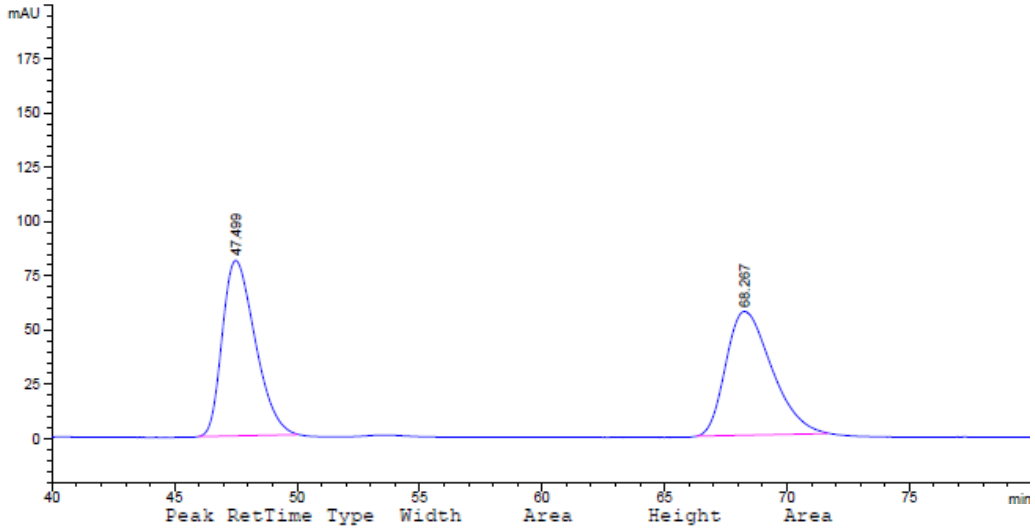
FTIR (neat): 3456, 3333, 2359, 1687, 1330, 1077, 712.

HPLC: (Chiralcel column OD-H, Hexane:2-PrOH = 95:5, 1.0 mL/min, 230 nm) ee = 86%.

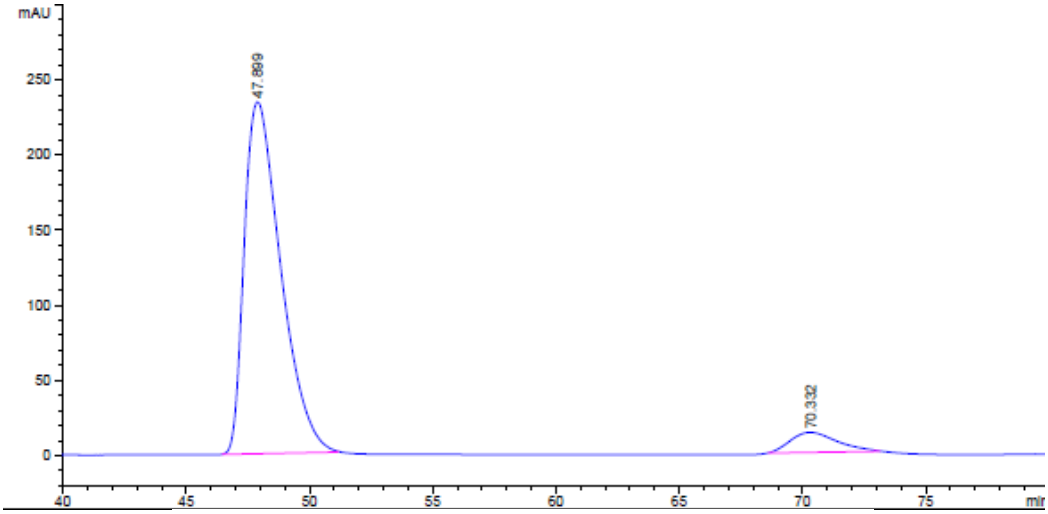
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = –7.9° (c = 0.95, $CHCl_3$).


OH
PhthN
3.3y
1H (500 MHz, CDCl3)
f1 (ppm)


OH
PhthN
3.3y
13C (125 MHz, CDCl3)
f1 (ppm)

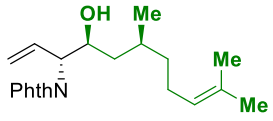


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.499	BB	1.3809	7560.30127	80.85515	50.3932
2	68.267	BB	1.6973	7442.33301	57.07264	49.6068



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.899	BB	1.5241	2.40848e4	234.12973	93.1743
2	70.332	BB	1.5583	1764.38269	13.32936	6.8257

2-((3*R*,4*S*,6*S*)-4-hydroxy-6,10-dimethylundeca-1,9-dien-3-yl)isoindoline-1,3-dione (3.3z)



3.3z

Alcohol **3.2z** (31.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 10:90 EtOAc:hexanes), the title compound **3.3z** (41.7 mg, 0.12 mmol, 10:1 dr) was obtained as a pale yellow oil in 62% yield.

TLC (SiO_2) R_f = 0.47 (20:80 EtOAc:hexanes)

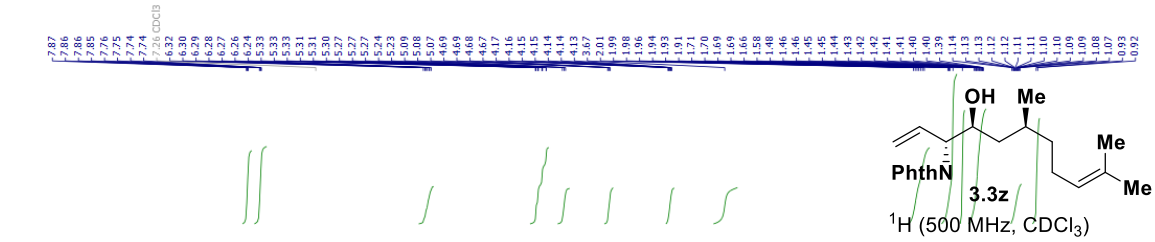
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.28 (ddd, *J* = 17.6, 10.4, 7.8 Hz, 1H), 5.32 (d, *J* = 10.7 Hz, 1H), 5.26 (d, *J* = 17.3 Hz, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 4.68 (dd, *J* = 7.8, 3.4 Hz, 1H), 4.15 (ddd, *J* = 8.6, 5.2, 3.5 Hz, 1H), 3.67 (brs, 1H), 2.04 – 1.88 (m, 1H), 1.73 – 1.66 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.50 – 1.39 (m, 3H), 1.15 – 1.07 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.9, 134.5, 131.8, 131.4, 131.1, 124.9, 123.7, 120.1, 70.6, 59.6, 41.6, 36.4, 29.3, 25.9, 25.5, 20.4, 17.8.

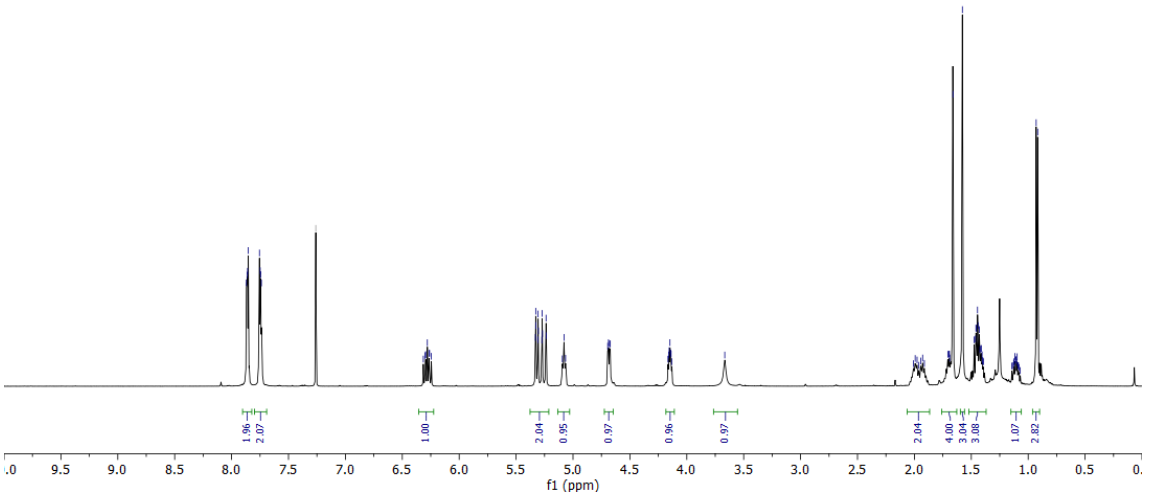
HRMS (Na+, *m/z*) for $C_{21}H_{27}NO_3$: calcd. = 364.1883; found = 364.1882.

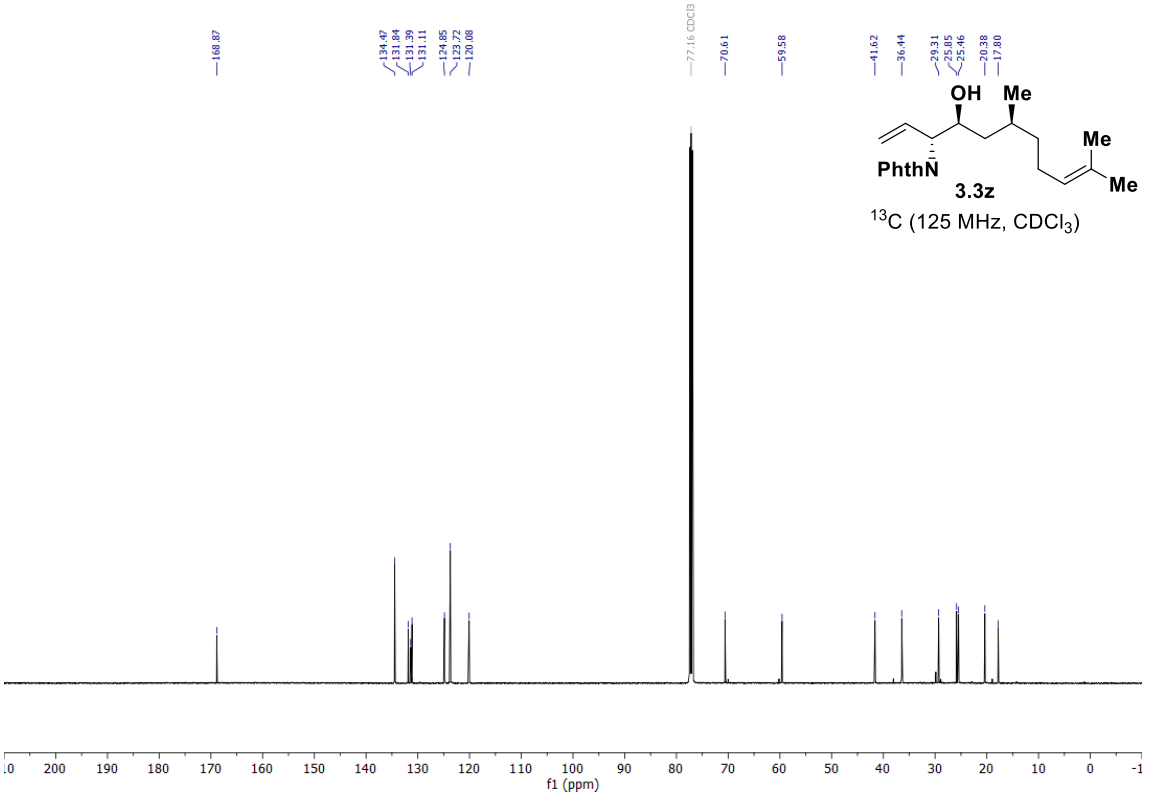
FTIR (neat): 3466, 2921, 1704, 1380, 1065, 719.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +39.5° (c = 1.37, $CHCl_3$).



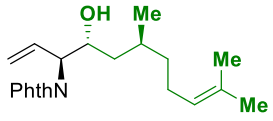
^{1}H (500 MHz, $CDCl_3$)





^{13}C (125 MHz, $CDCl_3$)

2-((3*S*,4*R*,6*S*)-4-hydroxy-6,10-dimethylundeca-1,9-dien-3-yl)isoindoline-1,3-dione (3.3a')



3.3a'

Alcohol **3.2a'** (31.2 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) using 5 mol% of (*S*)-Ir-**IV**. Upon flash column chromatography (SiO_2, 10:90 EtOAc:hexanes), the title compound **3.3a'** (43.1 mg, 0.13 mmol, 13:1 dr) was obtained as a pale yellow oil in 64% yield.

TLC (SiO_2) R_f = 0.47 (20:80 EtOAc:hexanes)

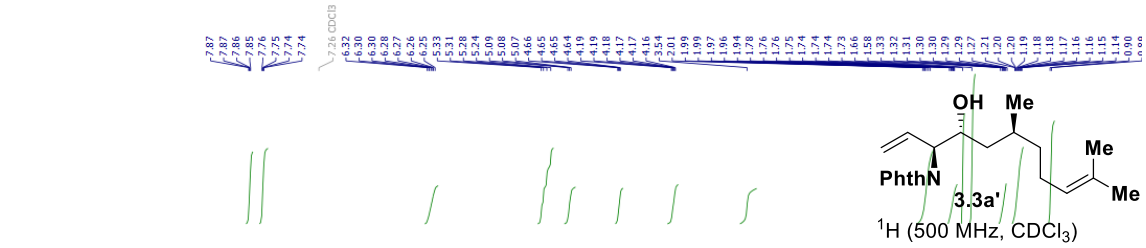
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.28 (ddd, *J* = 17.6, 10.4, 7.8 Hz, 1H), 5.32 (d, *J* = 10.7 Hz, 1H), 5.27 (d, *J* = 17.3 Hz, 1H), 5.08 (t, *J* = 7.1 Hz, 1H), 4.65 (dd, *J* = 7.8, 3.9 Hz, 1H), 4.18 (ddd, *J* = 10.3, 3.7 Hz, 1H), 3.54 (brs, 1H), 2.03 – 1.93 (m, 2H), 1.77 – 1.72 (m, 1H), 1.66 (s, 3H), 1.58 (brs, 4H), 1.34 – 1.28 (m, 1H), 1.21 – 1.14 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 3H).

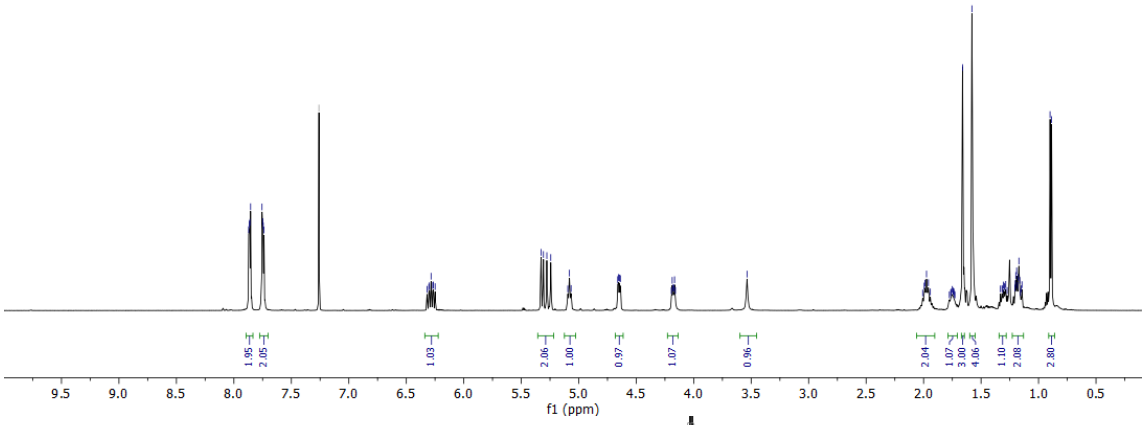
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 134.5, 131.9, 131.4, 131.4, 124.9, 123.7, 120.1, 70.0, 60.2, 41.7, 38.0, 27.9, 25.9, 25.6, 18.9, 17.8.

HRMS (Na+, *m/z*) for $C_{21}H_{27}NO_3$: calcd. = 364.1883; found = 364.1883.

FTIR (neat): 3454, 2923, 1703, 1381, 1066, 719.

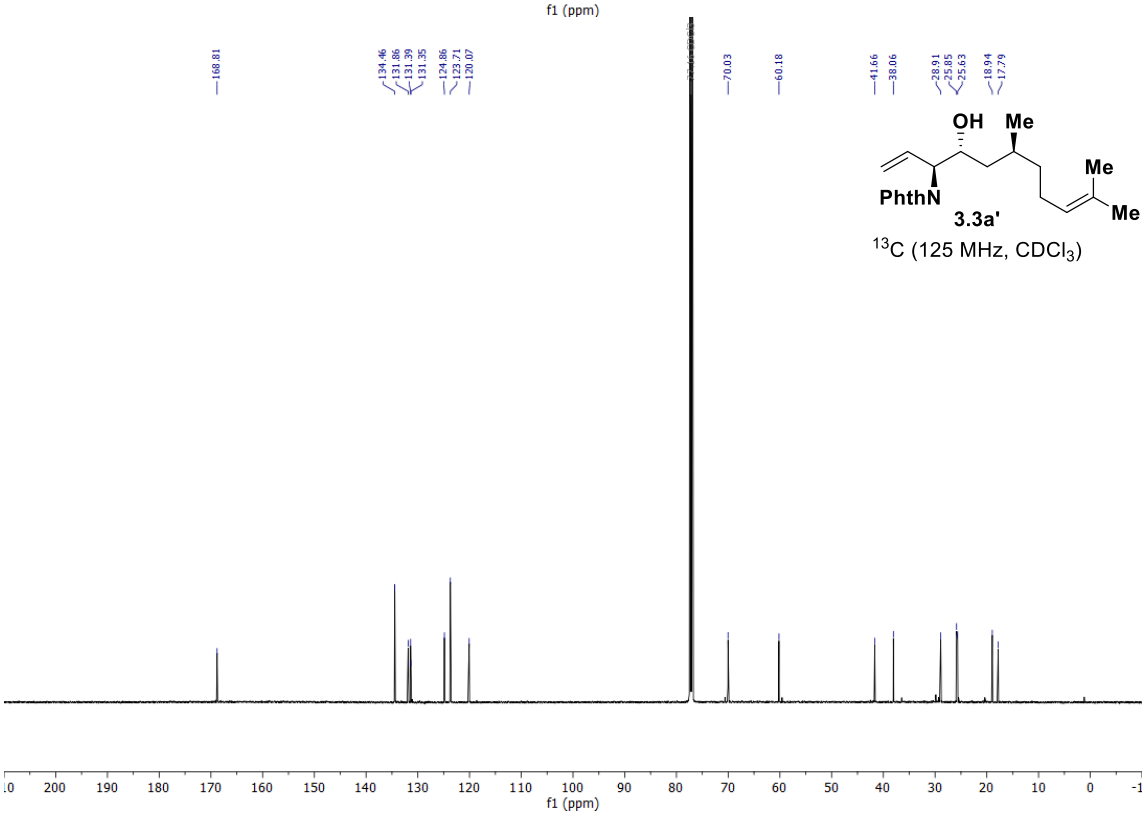
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = –18.2° (c = 1.44, $CHCl_3$).





OH Me
PhthN
Me
Me
3.3a'

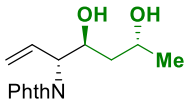
^{1}H (500 MHz, $CDCl_3$)



OH Me
PhthN
Me
Me
3.3a'

^{13}C (125 MHz, $CDCl_3$)

2-((3*R*,4*S*,6*R*)-4,6-dihydroxyhept-1-en-3-yl)isoindoline-1,3-dione (3.3b')



3.3b'

Alcohol **3.2b'** (18.0 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) using 7.5 mol% of (*R*)-**Ir-VI**. Upon flash column chromatography (SiO_2, 50:50 EtOAc:hexanes), the title compound **3.3b'** (39.6 mg, 0.14 mmol, 20:1 dr) was obtained as a white solid in 72% yield.

TLC (SiO_2) R_f = 0.38 (50:50 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.30 (ddd, *J* = 17.6, 10.4, 7.7 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 5.29 (d, *J* = 17.3 Hz, 1H), 4.71 (dd, *J* = 7.8, 4.4 Hz, 1H), 4.44 (dt, *J* = 9.8, 3.4 Hz, 1H), 4.20 – 4.13 (m, 1H), 1.77 (ddd, *J* = 14.3, 9.6, 2.9 Hz, 1H), 1.77 (ddd, *J* = 14.3, 8.4, 3.1 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H).

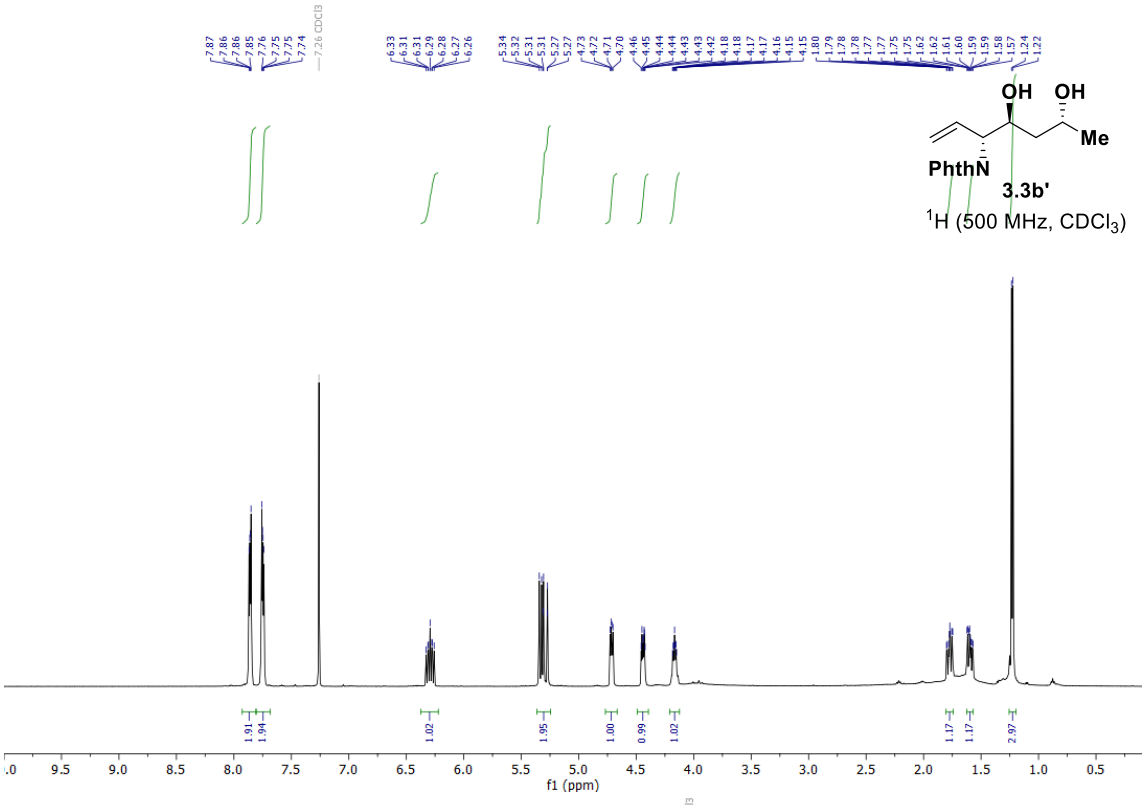
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 134.5, 131.8, 131.3, 123.8, 120.3, 69.6, 65.2, 59.5, 41.7, 23.7.

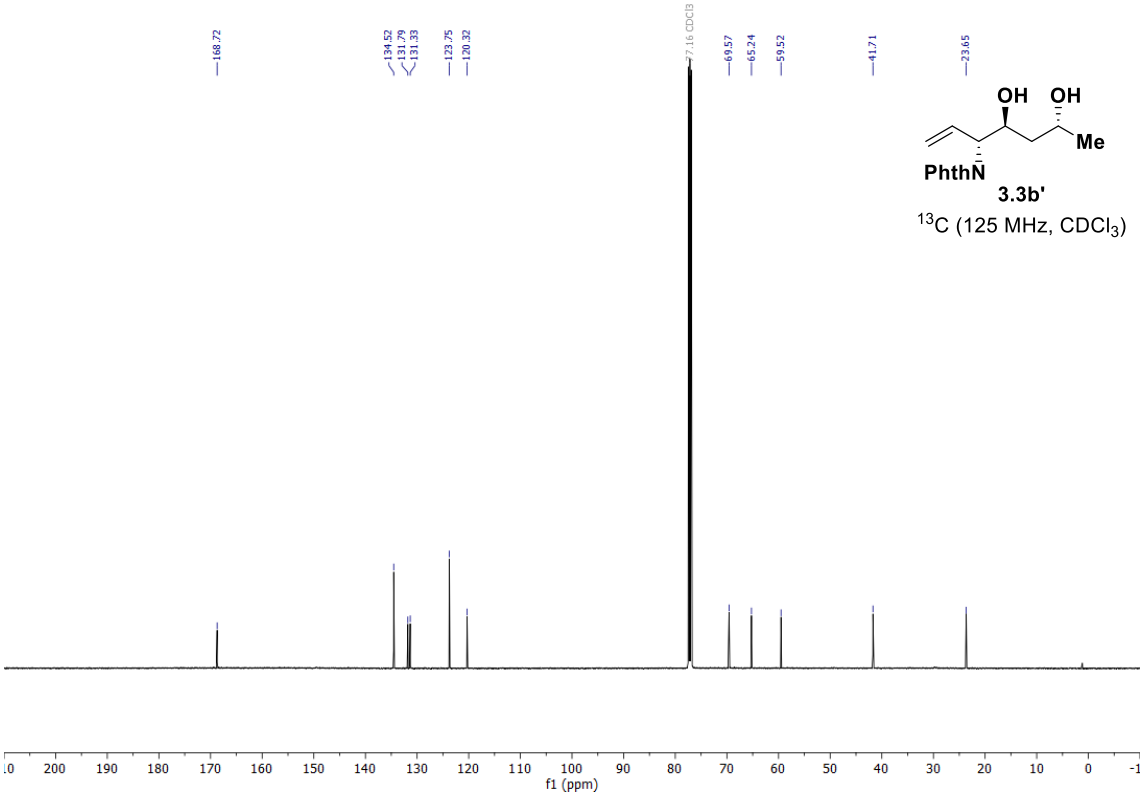
HRMS (Na+, *m/z*) for $C_{15}H_{17}NO_4$: calcd. = 298.1050; found = 298.1054.

FTIR (neat): 3457, 3378, 2963, 2359, 1693, 1386, 988, 890, 711.

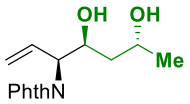
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +56.9° (c = 1.30, $CHCl_3$).

MP [123 – 127] °C


OH
OH
Me
PhthN
3.3b'
1H (500 MHz, CDCl3)
f1 (ppm)


OH
OH
Me
PhthN
3.3b'
13C (125 MHz, CDCl3)
f1 (ppm)

2-((3*S*,4*R*,6*R*)-4,6-dihydroxyhept-1-en-3-yl)isoindoline-1,3-dione (3.3c')



3.3c'

Alcohol **3.2c'** (18 mg, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h) using 7.5 mol% of (*S*)-Ir-**IV**. Upon flash column chromatography (SiO_2, 50:50 EtOAc:hexanes), the title compound **3.3c'** (36.3 mg, 0.13 mmol, 20:1 dr) was obtained as a white solid in 66% yield.

TLC (SiO_2) R_f = 0.38 (50:50 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.27 (ddd, *J* = 17.6, 10.4, 7.7 Hz, 1H), 5.34 (d, *J* = 10.7 Hz, 1H), 5.28 (d, *J* = 17.3 Hz, 1H), 4.67 (dd, *J* = 7.8, 3.8 Hz, 1H), 4.35 (dt, *J* = 10.9, 3.1 Hz, 1H), 4.10 – 4.03 (m, 1H), 1.72 (ddd, *J* = 14.2, 10.8, 9.4 Hz, 1H), 1.77 (dt, *J* = 14.2, 2.5 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H).

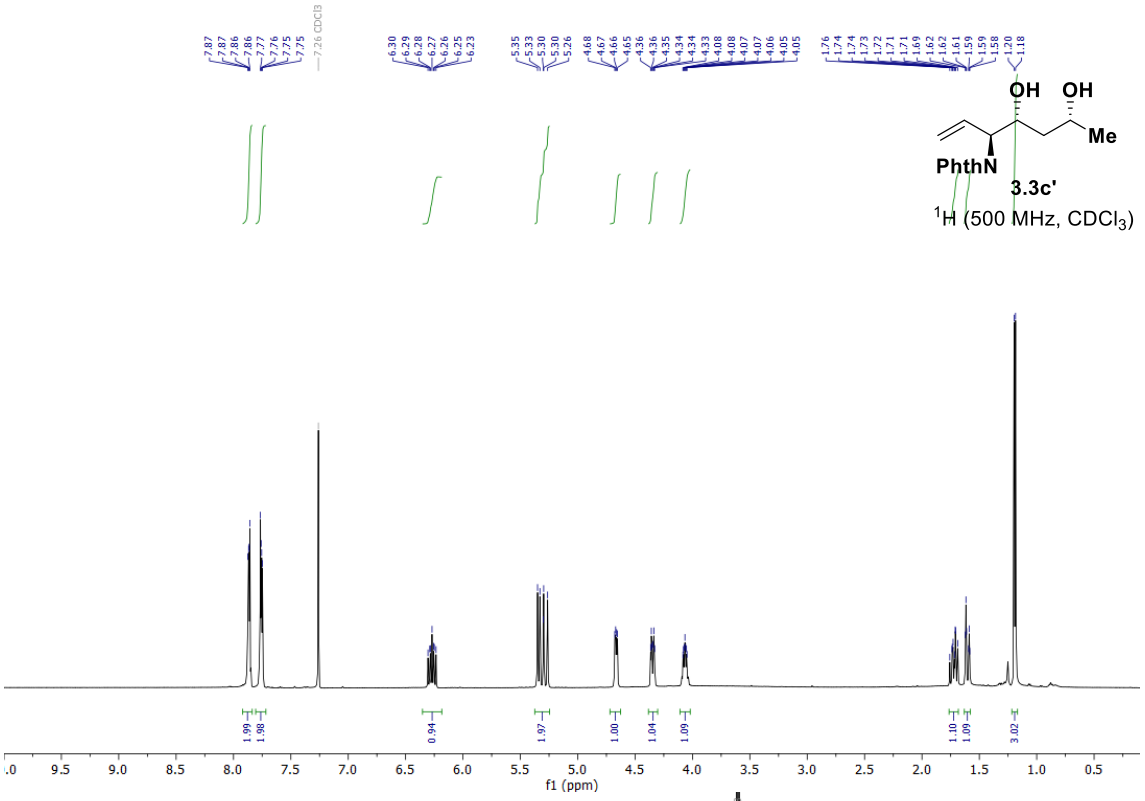
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 134.6, 131.8, 130.9, 123.8, 120.4, 73.4, 68.2, 59.8, 42.0, 23.8.

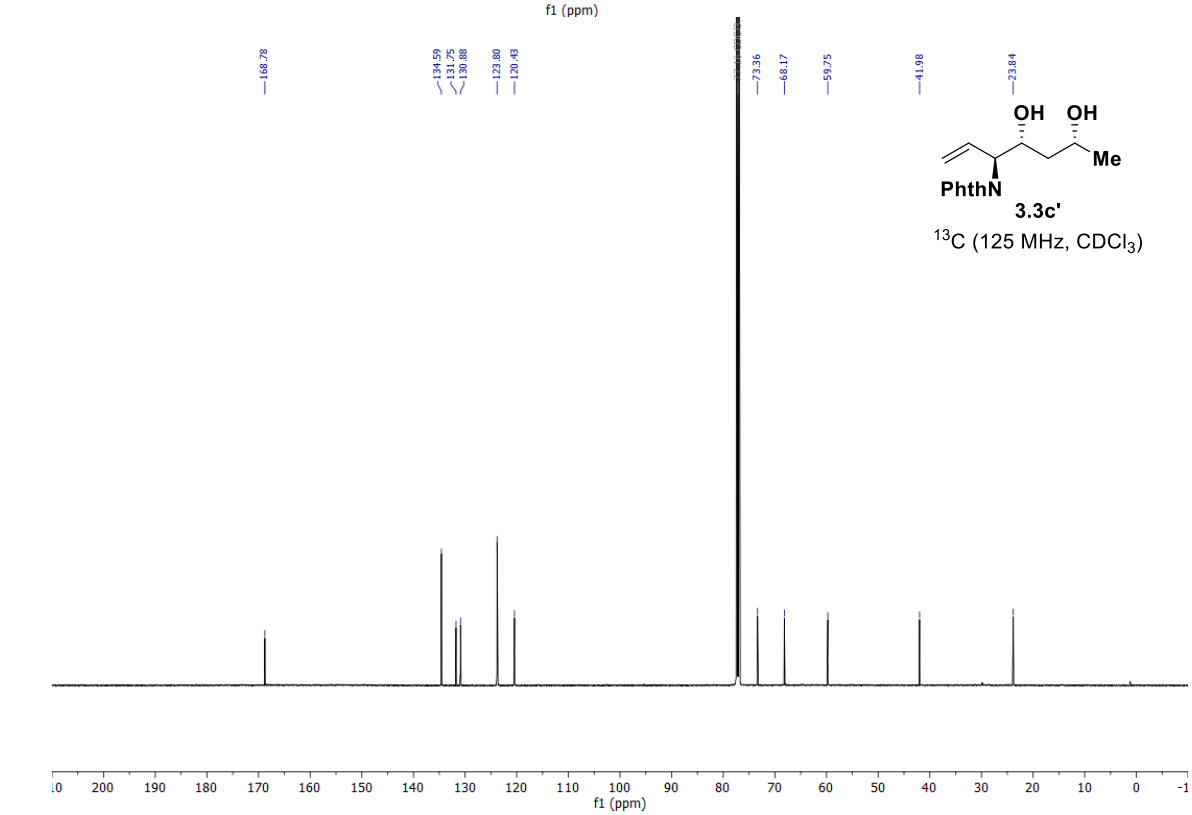
HRMS (Na+, *m/z*) for $C_{15}H_{17}NO_4$: calcd. = 298.1050; found = 298.1053.

FTIR (neat): 3197, 2966, 2360, 1699, 1381, 1323, 1073, 713.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = –76.1° (c = 0.90, $CHCl_3$).

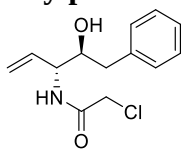
MP [108 – 111] °C


OH
OH
Me
PhthN
3.3c'
1H (500 MHz, CDCl3)
f1 (ppm)


OH
OH
Me
PhthN
3.3c'
13C (125 MHz, CDCl3)
f1 (ppm)

3.5.3.5 Procedures and Spectral Data of Product Elaborations

2-chloro-*N*-((3*R*,4*S*)-4-hydroxy-5-phenylpent-1-en-3-yl)acetamide (3.4a)



3.4a

To a round bottom flask charged with coupling product **3.3a** (92.2 mg, 0.3 mmol, 100 mol%) was added a solution of $N_2H_4 \bullet H_2O$ in DCM and MeOH (4:6:2, 12 mL) and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with water (5 mL) and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (6 x 10 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate followed by brine. The solution was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was then dissolved in DCM (2 mL, 0.15 M) and triethylamine added (81 µL, 0.6 mmol, 200 mol%). The reaction was stirred at -10 °C for 5 minutes and chloroacetyl chloride added dropwise (24 µL, 0.6 mmol, 200 mol%). The reaction mixture was stirred at -10 °C for 30 minutes and then quenched by addition of a saturated solution of ammonium chloride. The mixture was then diluted with EtOAc and the mixture transferred to a separatory funnel. The phases were separated and the organic layer was washed with saturated solutions of ammonium chloride and sodium bicarbonate followed by brine. The solution was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 60:40 EtOAC:hexanes) to yield the title compound **3.4a** (62.4 mg, 0.25 mmol, >20:1 dr) as a white solid in 82% yield.

TLC (SiO_2) R_f = 0.28 (60:40 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.31 (m, 2H), 7.26 – 7.20 (m, 3H), 7.10 (d, *J* = 7.7 Hz, 1H), 5.97 (ddd, *J* = 17.3, 10.5, 7.0 Hz, 1H), 5.38 – 5.33 (m, 2H), 4.56 – 4.52 (m, 2H), 4.06 (brs, 2H), 3.99 (dt, *J* = 9.4, 3.7 Hz, 1H), 2.82 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.71 (dt, *J* = 13.8, 9.4 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H).

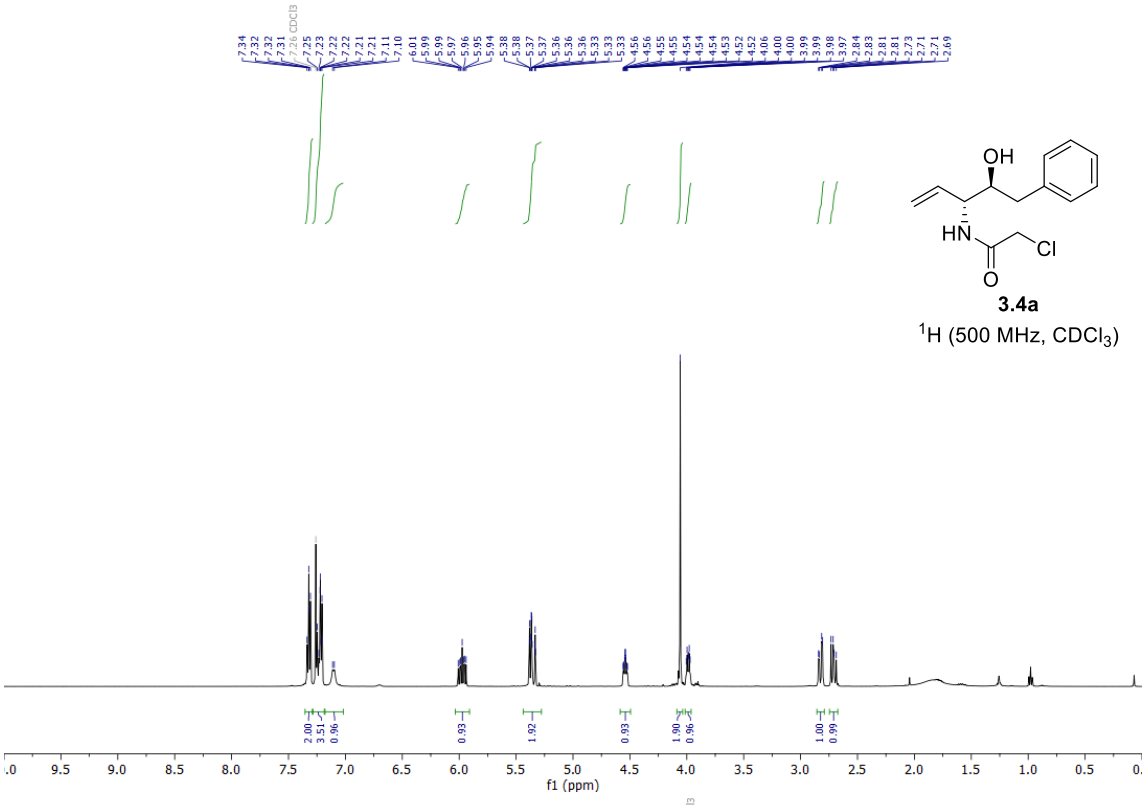
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 137.5, 132.3, 129.4, 129.0, 127.0, 119.3, 74.4, 56.3, 42.8, 40.7.

HRMS (Na+, *m/z*) for $C_{13}H_{16}ClNO_2$: calcd. = 276.0762; found = 276.0767.

FTIR (neat): 3289, 2918, 1640, 1533, 1267, 1053, 936, 752, 699.

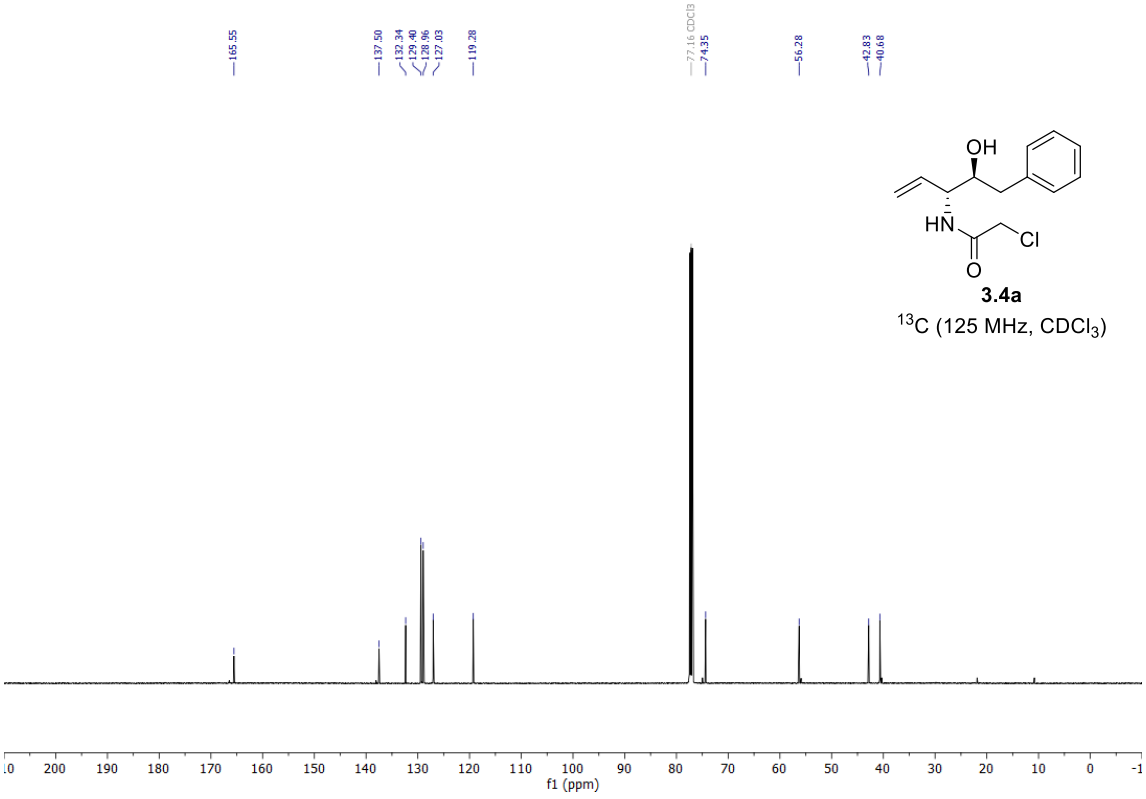
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +37.1° (c = 0.93, $CHCl_3$).

MP [81 – 85] °C



3.4a

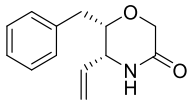
^{1}H (500 MHz, $CDCl_3$)



3.4a

^{13}C (125 MHz, $CDCl_3$)

(5*R*,6*S*)-6-benzyl-5-vinylmorpholin-3-one (3.8a)



3.8a

To a flame dried round bottomed flask charged with **3.4a** (52.7 mg, 0.21 mmol, 100 mol%) in THF (0.084 M) was added DMF (0.5 mL). The reaction mixture was stirred at 0 °C for 5 minutes before addition of NaH (60% w/w, 21 mg, 0.52 mmol, 250 mol%). The mixture was then stirred at 0 °C for 40 minutes. Saturated solution of ammonium chloride and EtOAC were then added and the reaction mixture transferred to a separatory funnel. The phases were separated and the organic phase washed with saturated solutions of ammonium chloride and sodium bicarbonate followed by brine. The solution was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 70:30 EtOAC:hexanes) to yield the title compound **3.8a** (33.6 mg, 0.15 mmol, >20:1 dr) as a pale-yellow oil in 74% yield.

TLC (SiO_2) R_f = 0.42 (80:20 EtOAc:hexanes)

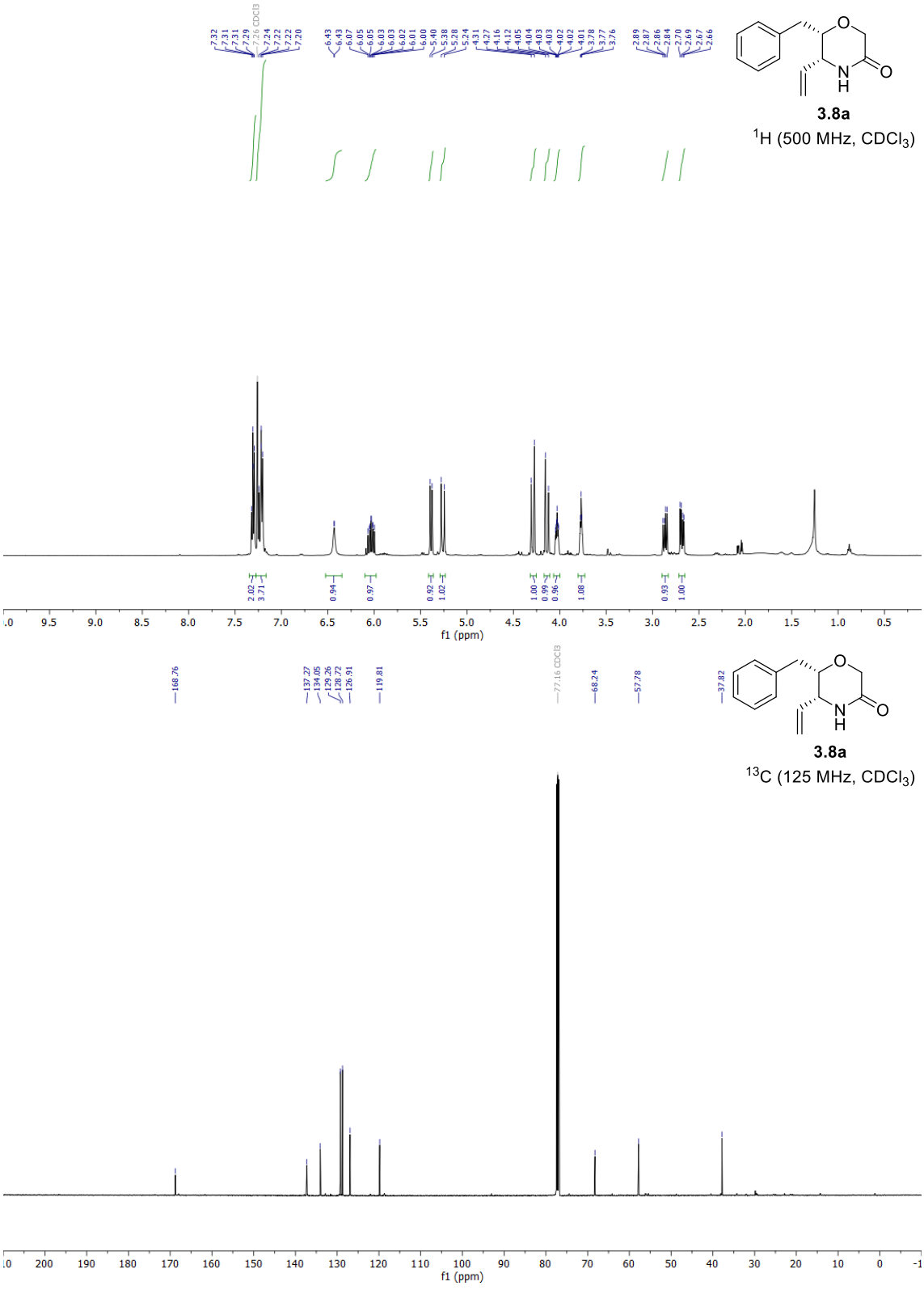
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 – 7.29 (m, 2H), 7.26 – 7.20 (m, 3H), 6.42 (brs, 1H), 5.97 (ddd, *J* = 17.4, 10.1, 7.9 Hz, 1H), 5.39 (d, *J* = 10.2 Hz, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 4.29 (d, *J* = 16.9 Hz, 1H), 4.14 (d, *J* = 16.9 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.78 – 3.75 (m, 1H), 2.87 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.68 (dd, *J* = 14.3, 5.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 137.3, 134.1, 129.3, 128.7, 126.9, 119.8, 68.2, 57.8, 37.8.

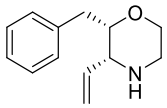
HRMS (H+, *m/z*) for $C_{13}H_{15}NO_2$: calcd. = 218.1176; found = 218.1175.

FTIR (neat): 3217, 3028, 2923, 1668, 1420, 1112, 740, 699.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = +64.8° (c = 1.18, $CHCl_3$).


7.32
7.31
7.31
7.29
7.26 CDCl3
7.24
7.22
7.20
6.43
6.43
6.07
6.05
6.05
6.03
6.03
6.02
6.01
6.00
5.40
5.38
5.28
5.24
4.31
4.27
4.16
4.12
4.05
4.04
4.03
4.03
4.02
4.02
4.01
3.78
3.77
3.76
2.89
2.87
2.86
2.84
2.70
2.69
2.67
2.66
O
N
H
O
3.8a
1H (500 MHz, CDCl3)
2.02
3.71
0.94
0.97
0.92
1.02
1.00
0.99
0.96
1.08
0.93
1.00
f1 (ppm)
168.76
137.27
134.05
129.26
128.72
126.91
119.81
77.16 CDCl3
68.24
57.78
37.82
O
N
H
O
3.8a
13C (125 MHz, CDCl3)
f1 (ppm)

(2*S*,3*R*)-2-benzyl-3-vinylmorpholine (3.5a)



3.5a

To a flame dried round bottomed flask charged with $LiAlH_4$ (20 mg, 0.30 mmol, 300 mol%) in THF (0.05 M) was added **3.8a** (21.7 mg, 0.1 mmol, 100 mol%) in THF (0.05 M) at 0 °C. The reaction mixture was stirred reflux for 6 hours. Water (30 µL), NaOH (10% aq. Solution, 30 µL), and MgSO4 added to the reaction mixture. The resulting mixture was filtered over a celite plug, washed with MeOH, and the solvent removed *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, 95:5 DCM:MeOH) to yield the title compound **3.5a** (14.6 mg, 0.07 mmol, >20:1 dr) as a pale-yellow oil in 72% yield.

TLC (SiO_2) R_f = 0.22 (95:5 DCM:MeOH)

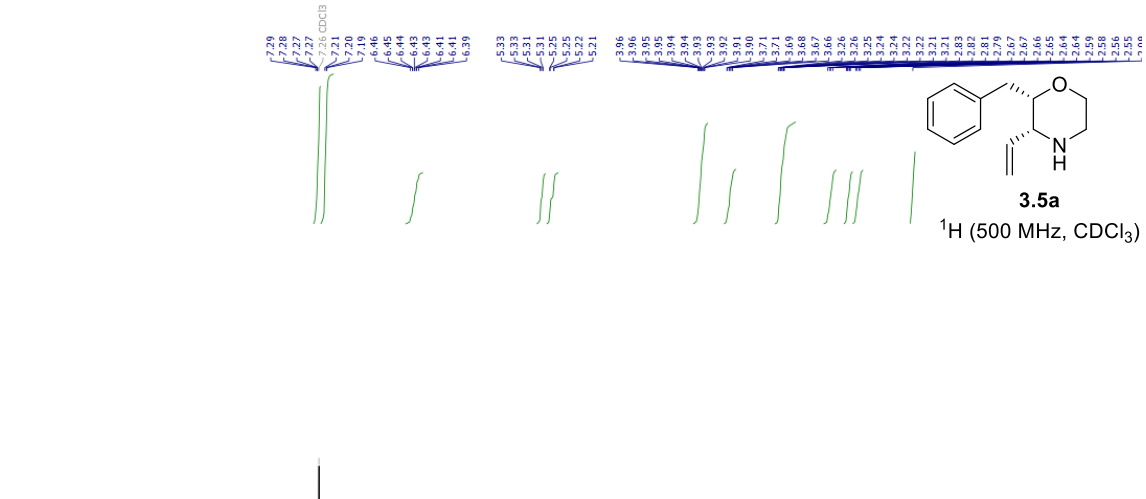
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 – 7.26 (m, 2H), 7.21 – 7.19 (m, 3H), 6.43 (dt, *J* = 17.1, 9.6 Hz, 1H), 5.33 (d, *J* = 9.7 Hz, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 3.96 (ddd, *J* = 8.4, 6.0, 2.6 Hz, 1H), 3.93 (dt, *J* = 11.5, 3.0 Hz, 1H), 3.69 (td, *J* = 11.1, 2.8 Hz, 1H), 3.25 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.21 (td, *J* = 11.4, 3.6 Hz, 1H), 2.81 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.66 (dt, *J* = 12.2, 2.8 Hz, 1H), 2.57 (dd, *J* = 14.2, 6.0 Hz, 1H), 2.09 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.2, 134.2, 129.4, 128.5, 126.4, 119.6, 79.1, 67.1, 58.7, 40.6, 38.3.

HRMS (H+, *m/z*) for $C_{13}H_{17}NO$: calcd. = 204.1383; found = 204.1387.

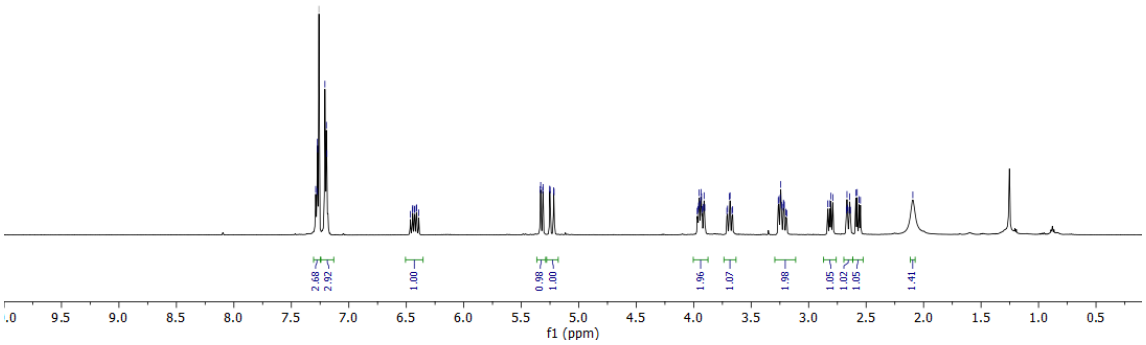
FTIR (neat): 2921, 2854, 1454, 1085, 923, 698.

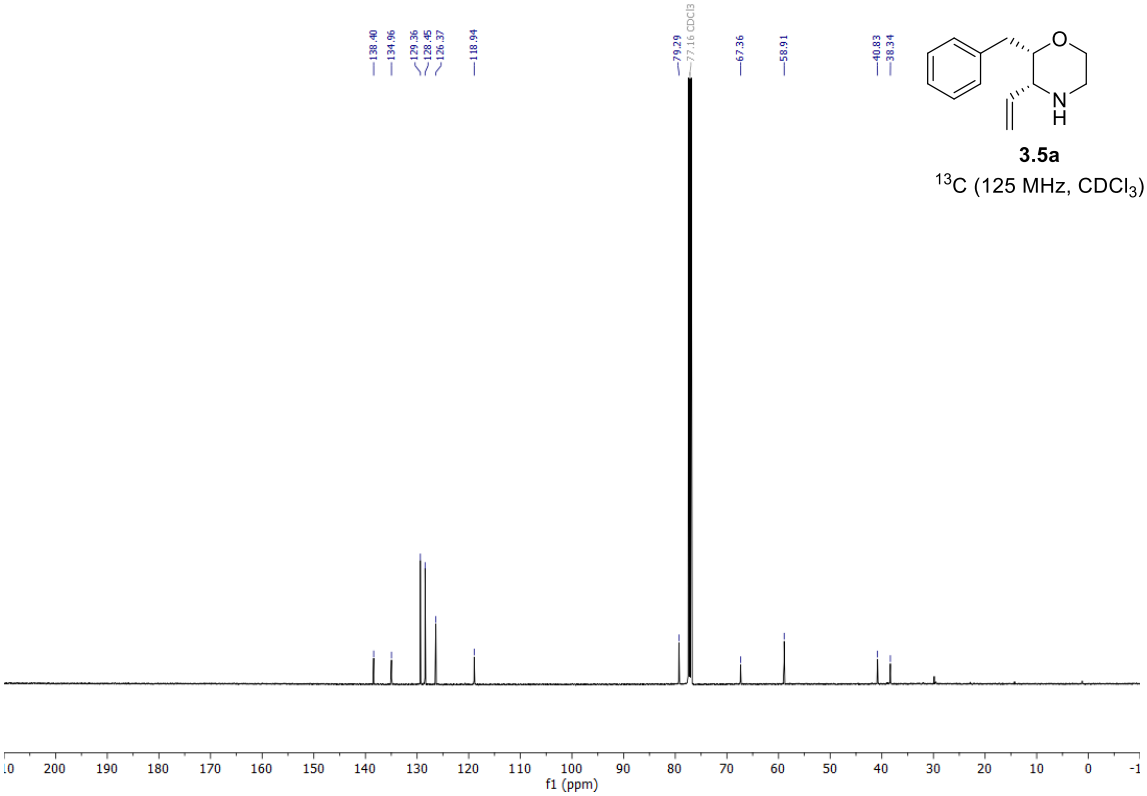
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{34}}$ = –8.2° (c = 0.79, $CHCl_3$).



3.5a

^{1}H (500 MHz, $CDCl_3$)

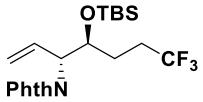




3.5a

^{13}C (125 MHz, $CDCl_3$)

2-((3*R*,4*S*)-4-((tert-butyldimethylsilyl)oxy)-7,7,7-trifluorohept-1-en-3-yl)isoindoline-1,3-dione (3.9m)



3.9m

To a solution of alcohol **3.3m** (50.0 mg, 0.117 mmol, 100 mol%) in dried DMF (220 µL) was added Et_3N (82 µL, 0.585 mmol, 500 mol%), TBSCl (44.0 mg, 0.293 mmol, 250 mol%) and 4-(dimethylamino)pyridine (2.9 mg, 0.0232 mmol, 20 mol%). The reaction was heated to 45 °C for 48 h. The contents were diluted with CH_2Cl_2 (2 mL) and washed with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was subjected to flash chromatography on silica (EtOAc:hexanes 10:90) to furnish the title compound **3.9m** (43.5 mg, 0.102 mmol) in 87% yield as a clear oil.

TLC (SiO_2) R_f = 0.26 (10:90 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.25 (ddd, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.25 – 5.22 (m, 2H), 4.62 – 4.55 (m, 2H), 2.35 – 2.24 (m, 1H), 2.21 – 2.10 (m, 1H), 1.80 – 1.73 (m, 1H), 1.61 – 1.54 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

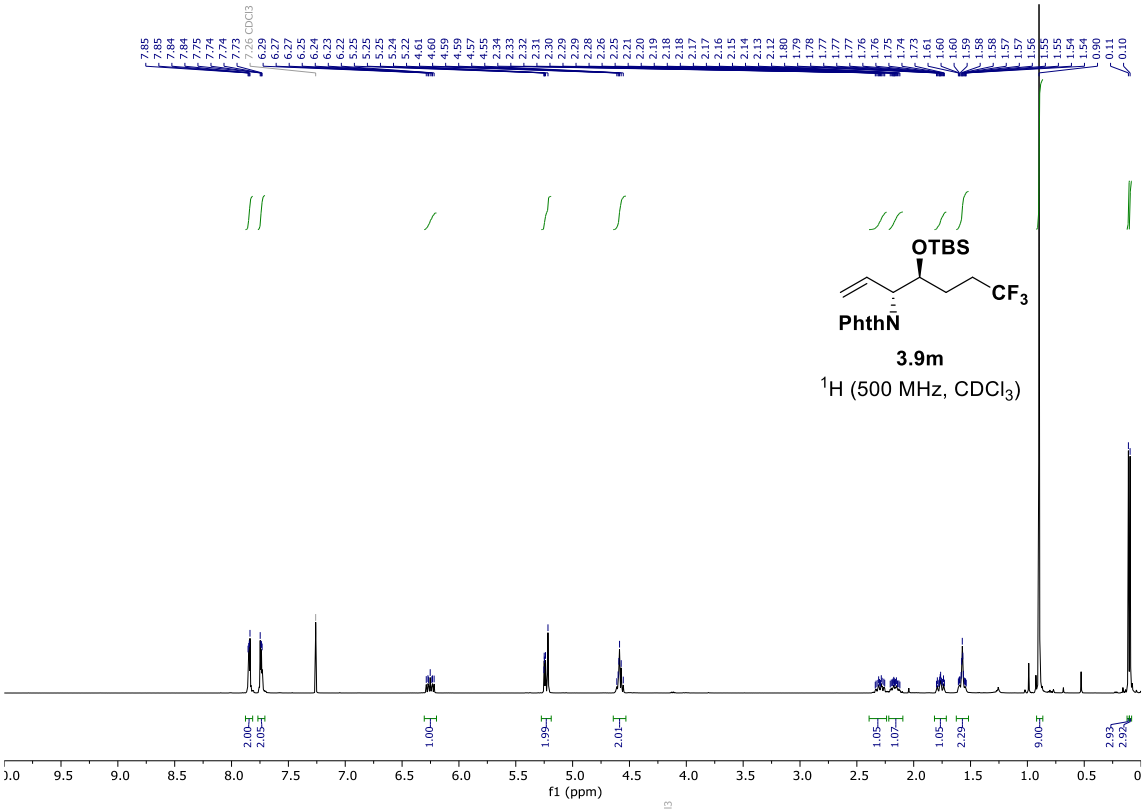
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.0, 134.4, 133.4, 131.8, 127.6 (q, *J* = 275.8 Hz), 123.6, 120.0, 68.9, 57.1, 27.6 (q, *J* = 29.0 Hz), 25.9, 18.1, – 4.2, – 4.2.

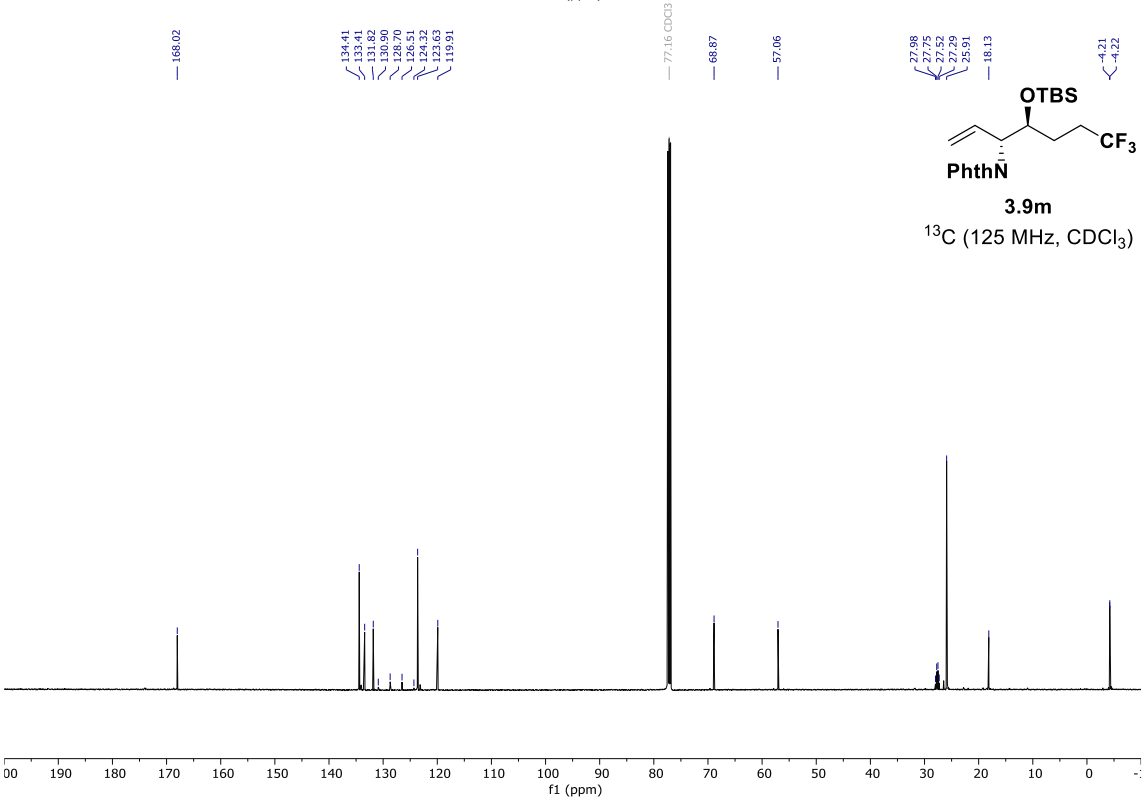
^{19}F NMR (470 MHz, $CDCl_3$) δ: -66.5 (t, *J* = 10.8 Hz).

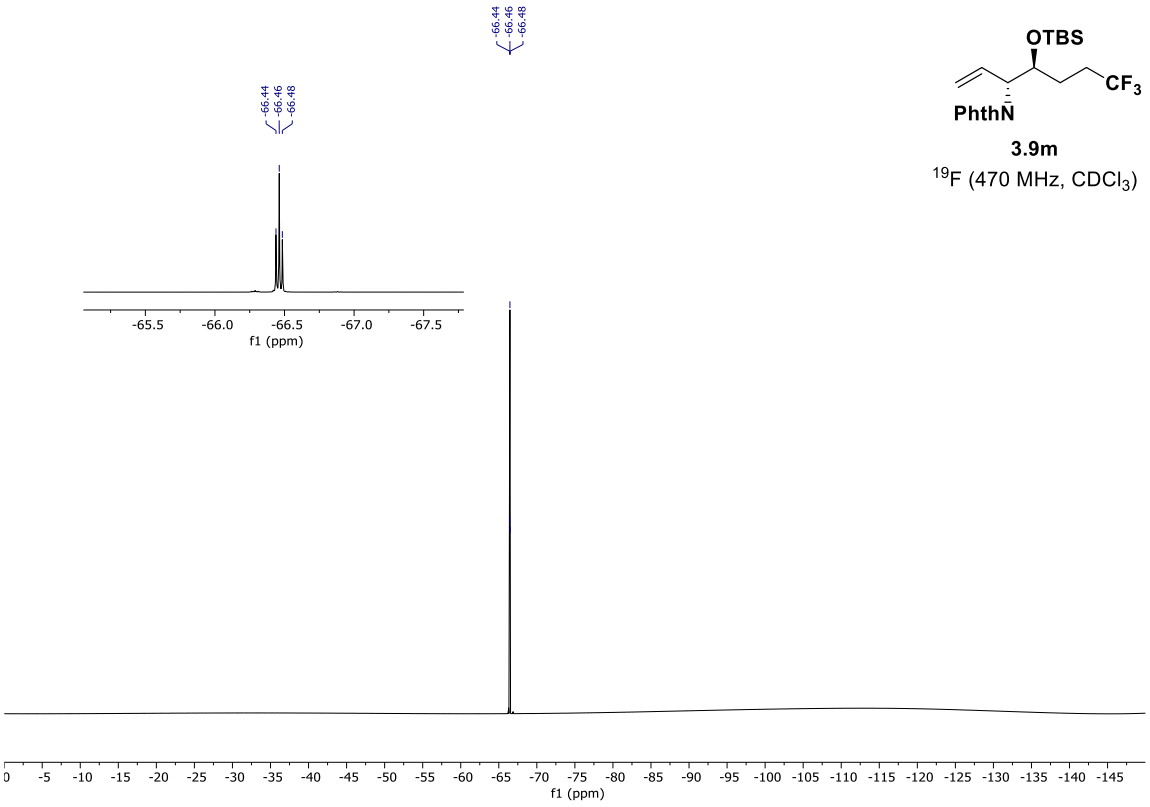
HRMS (Na+, *m/z*) for $C_{21}H_{28}F_3NO_3Si$: calcd. = 450.1683; found =450.1686.

FTIR (neat): 2956, 2931, 2858, 1716, 1379, 1254, 1060, 834, 717.

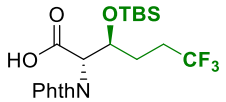
$[\alpha]_D^{24}$ = +52.2° (c = 1.13, $CHCl_3$).


OTBS
CF3
PhthN
3.9m
1H (500 MHz, CDCl3)
f1 (ppm)


OTBS
CF3
PhthN
3.9m
13C (125 MHz, CDCl3)
f1 (ppm)


-66.44
-66.46
-66.48
OTBS
CF3
PhthN
3.9m
19F (470 MHz, CDCl3)
-65.5
-66.0
-66.5
-67.0
-67.5
f1 (ppm)
0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)

(2*S*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-(1,3-dioxoisoindolin-2-yl)-6,6,6-trifluorohexanoic acid (3.6m)



3.6m

To a stirred solution of **3.9m** (100.0 mg, 0.230 mmol, 100 mol%), in 0.650 mL CCl_4, 0.650 mL CH_3CN, and 1.0 mL H_2O was added $NaIO_4$ (201.2 mg, 0.940 mmol, 400 mol%). After all the $NaIO_4$ had dissolved, $RuCl_3.H_2O$ (4.8 mg, 0.023 mmol, 10 mol%) was added, and the reaction mixture was stirred vigorously for 24 h at 25 °C. The contents were diluted with DCM (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was subjected to flash chromatography on silica (Hexanes/MeOH 90:10) to furnish the title compound **3.6m** (59.2 mg, 0.136 mmol) in 59% yield as a white solid.

TLC (SiO_2) R_f = 0.22 (10:90 MeOH:DCM)

^{1}H NMR (500 MHz, MeOD) δ: 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H), 4.73 – 4.70 (m, 1H), 2.28 – 2.13 (m, 2H), 2.10 – 2.03 (m, 1H), 1.62 – 1.54 (m, 1H), 0.85 (s, 9H), 0.23 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (125 MHz, MeOD) δ: 170.2, 168.0, 134.4, 131.6, 127.3 (q, *J* = 275.8 Hz), 122.9, 78.1, 70.0, 30.0 (q, *J* = 29.0 Hz), 26.4, 24.9, 17.4, – 5.7, – 6.0.

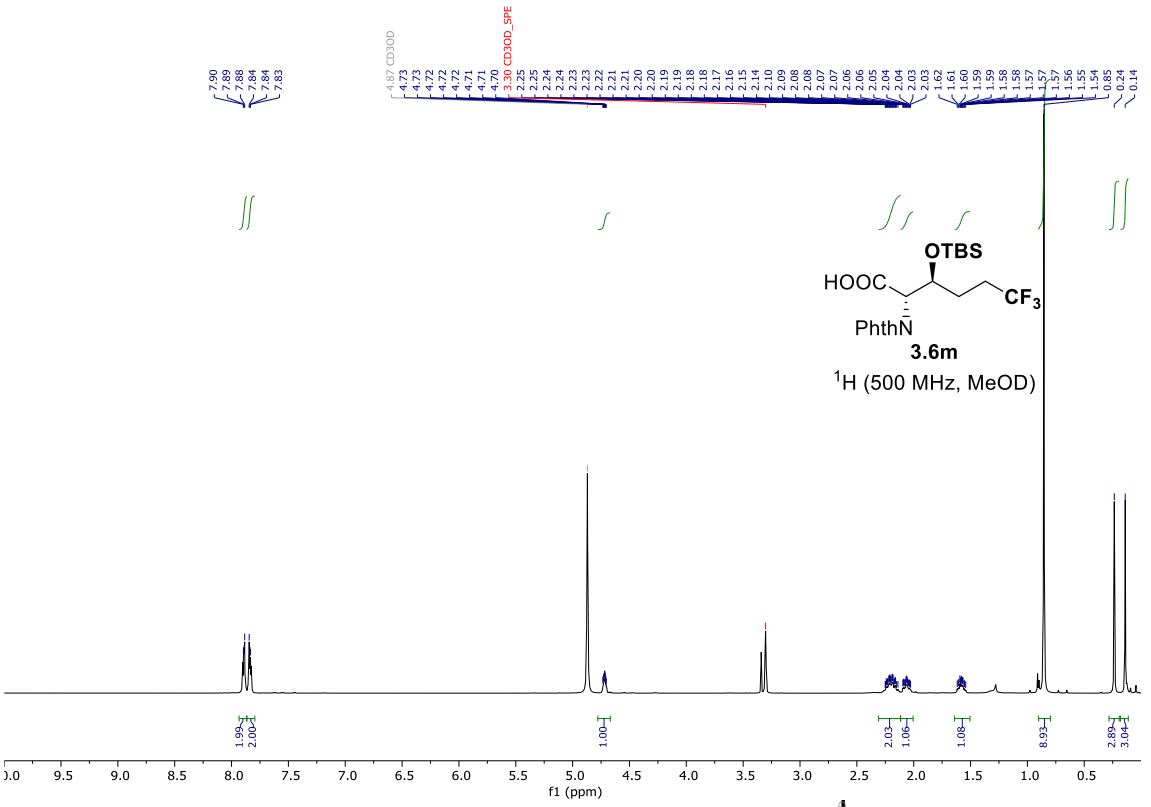
^{19}F NMR (470 MHz, MeOD) δ: -68.0 (t, *J* = 10.8 Hz).

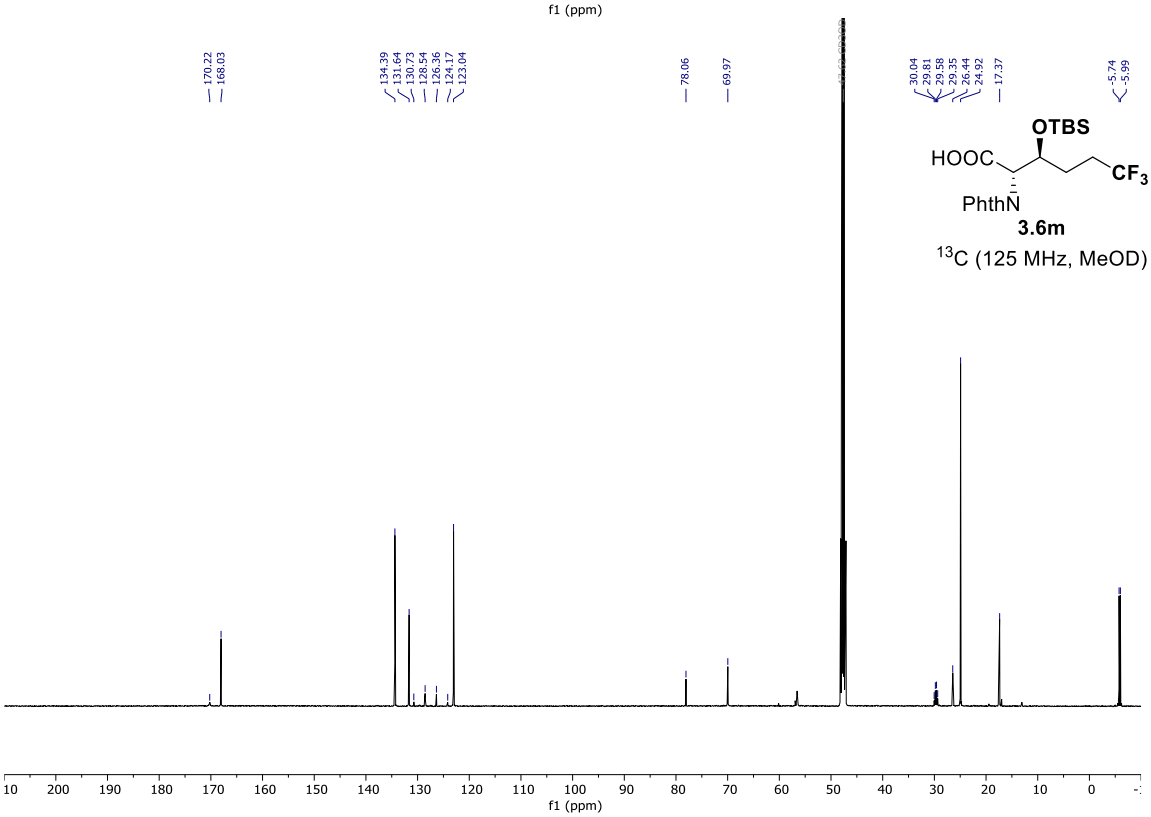
HRMS (Na+, *m/z*) for $C_{20}H_{26}F_3NO_5Si$: calcd. = 468.1425; found =468.1425.

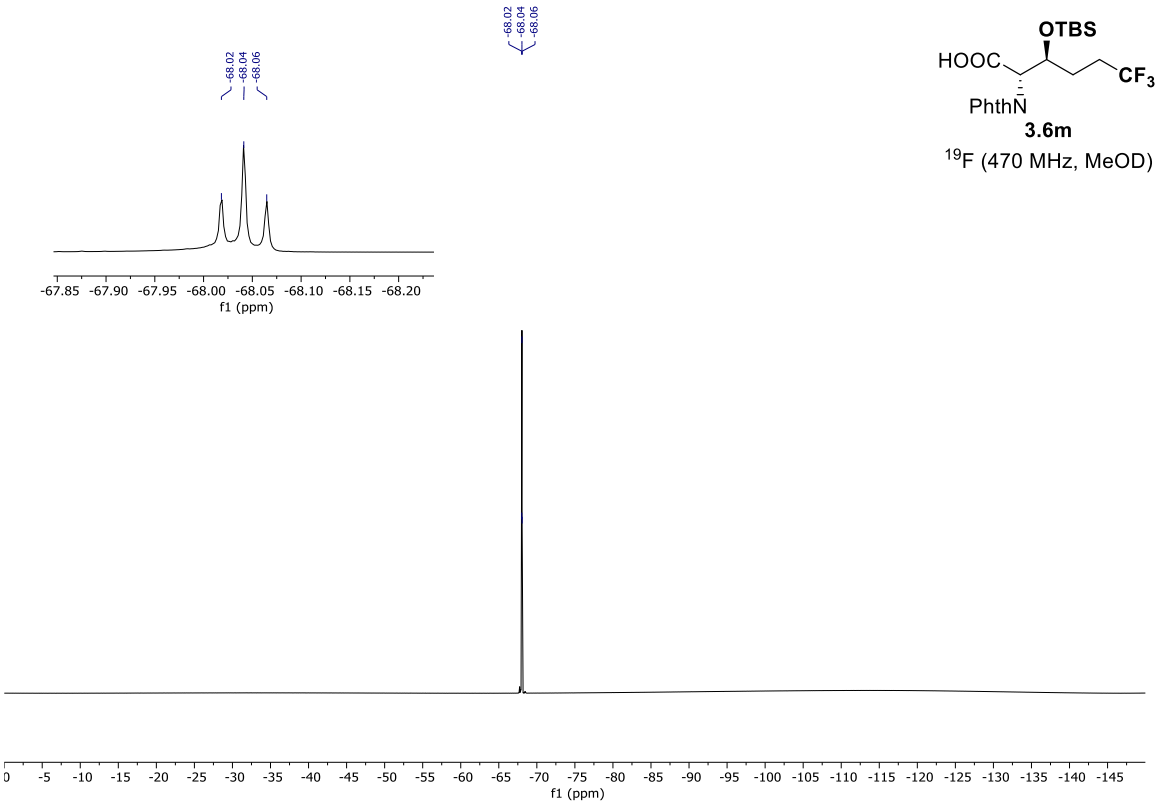
FTIR (neat): 2935, 2360, 1720, 1385, 1253, 1066, 835, 777, 721.

$[\alpha]_D^{24}$ = –31.1° (c = 1.83, $CHCl_3$).

MP [62 – 65] °C


OTBS
HOOC
CF3
PhthN
3.6m
1H (500 MHz, MeOD)
f1 (ppm)


OTBS
HOOC
CF3
PhthN
3.6m
13C (125 MHz, MeOD)
f1 (ppm)

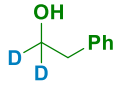


3.6m

^{19}F (470 MHz, MeOD)

3.5.3.6 Isotopic Labeling Studies

2-phenylethan-1,1-d$_2$-1-ol (*deuterio*-3.2a)



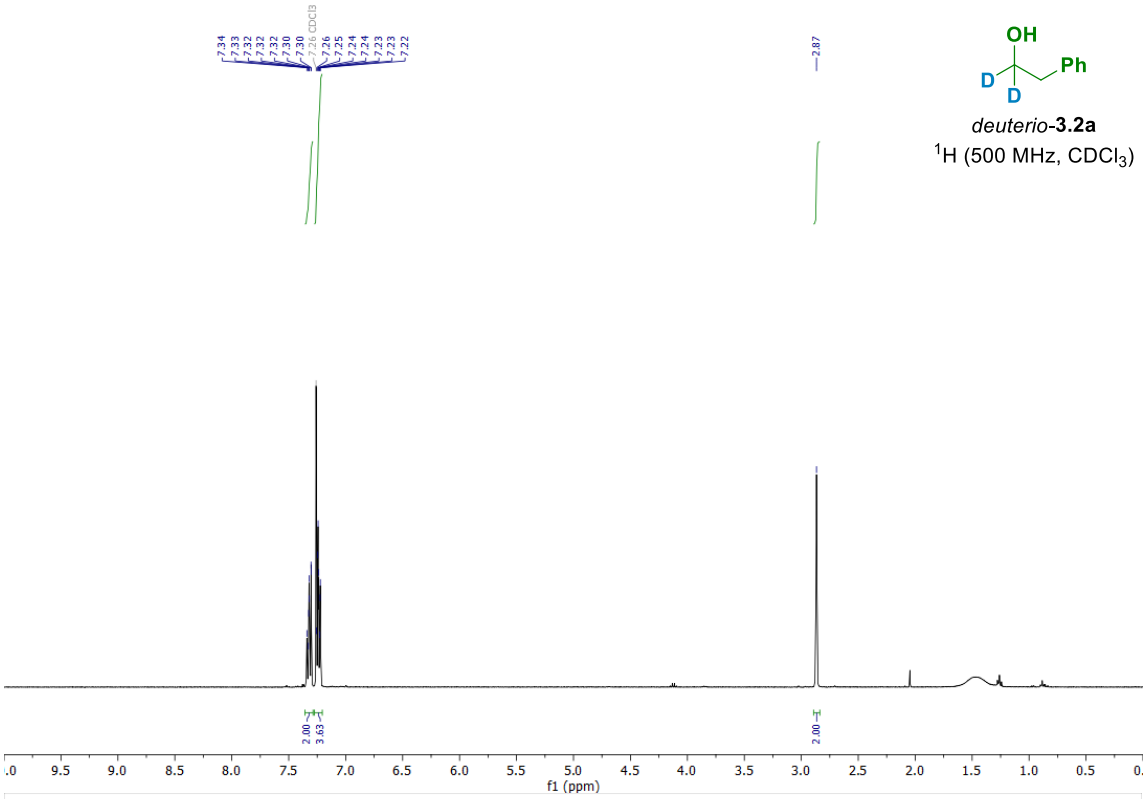
deuterio-**3.2a**

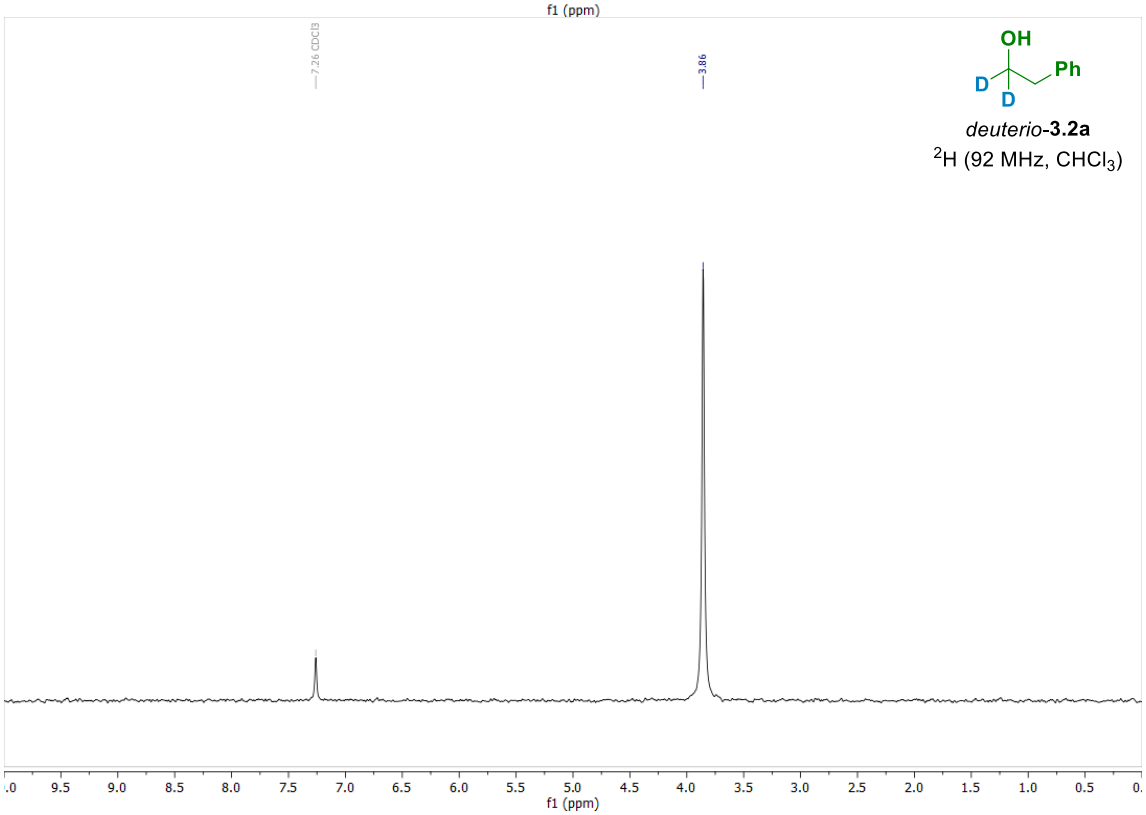
The title compound was synthesized over one step from 2-phenylacetic acid following literature procedures.[25]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.30 (m, 2H), 7.26 – 7.22 (m, 3H), 2.86 (brs, 2H)

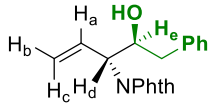
^{2}H NMR (92 MHz, $CHCl_3$) δ: 3.86 (brs, 2D)

HRMS (H+, *m/z*) for $C_8H_8D_2O$: calcd. = 124.0857; found = 124.0861.


7.34
7.33
7.32
7.32
7.32
7.30
7.30
7.26 CDCl3
7.26
7.25
7.24
7.24
7.23
7.23
7.22
2.87
OH
Ph
D
D
deuterio-3.2a
1H (500 MHz, CDCl3)
2.00
3.63
2.00
f1 (ppm)


7.26 CDCl3
3.86
OH
Ph
D
D
deuterio-3.2a
2H (92 MHz, CHCl3)
f1 (ppm)

2-((3*R*,4*S*)-4-hydroxy-5-phenylpent-1-en-3-yl)isoindoline-1,3-dione-d (*deuterio*-3.3a)



deuterio-**3.3a**
H_a (60% ^2H), H_b,H_c (25% ^2H)
H_d (<1% ^2H), H_e (>99% ^2H)

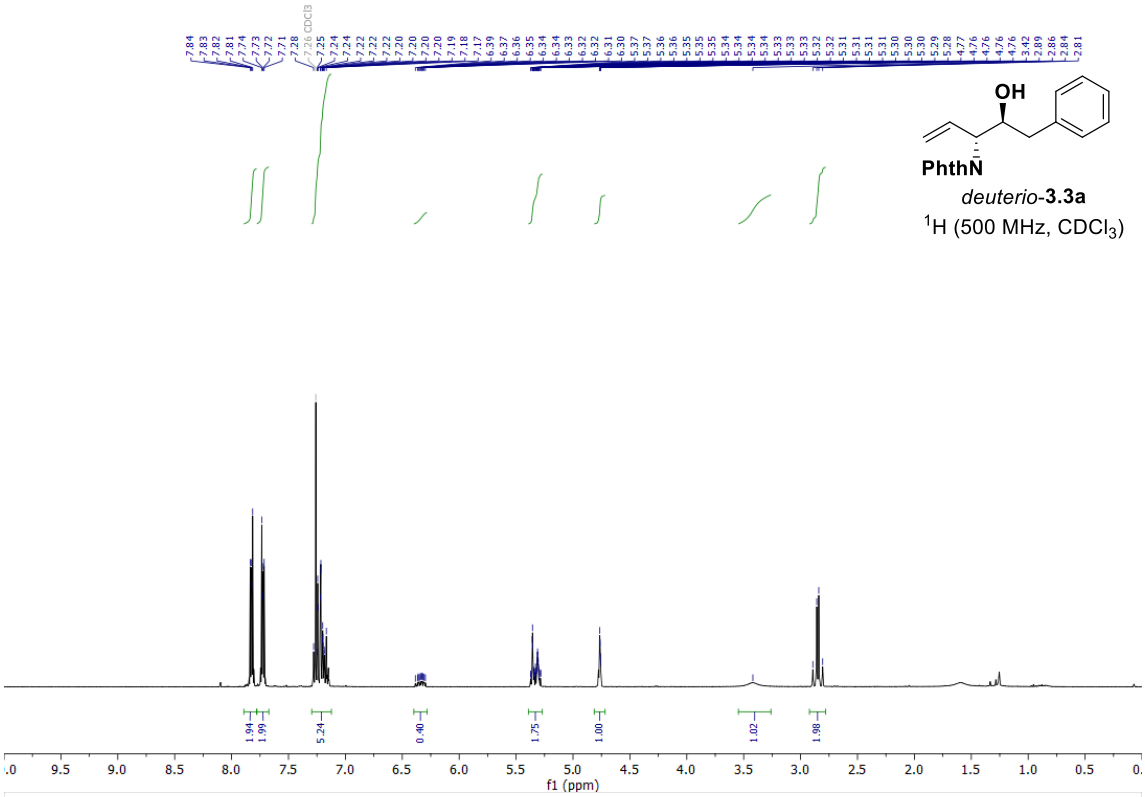
Alcohol *deuterio*-**3.2a** (24.0 µL, 0.2 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), the title compound *deuterio*-**3.3a** (41.8 mg, 0.14 mmol, >20:1 dr) was obtained as a light yellow solid in 68% yield.

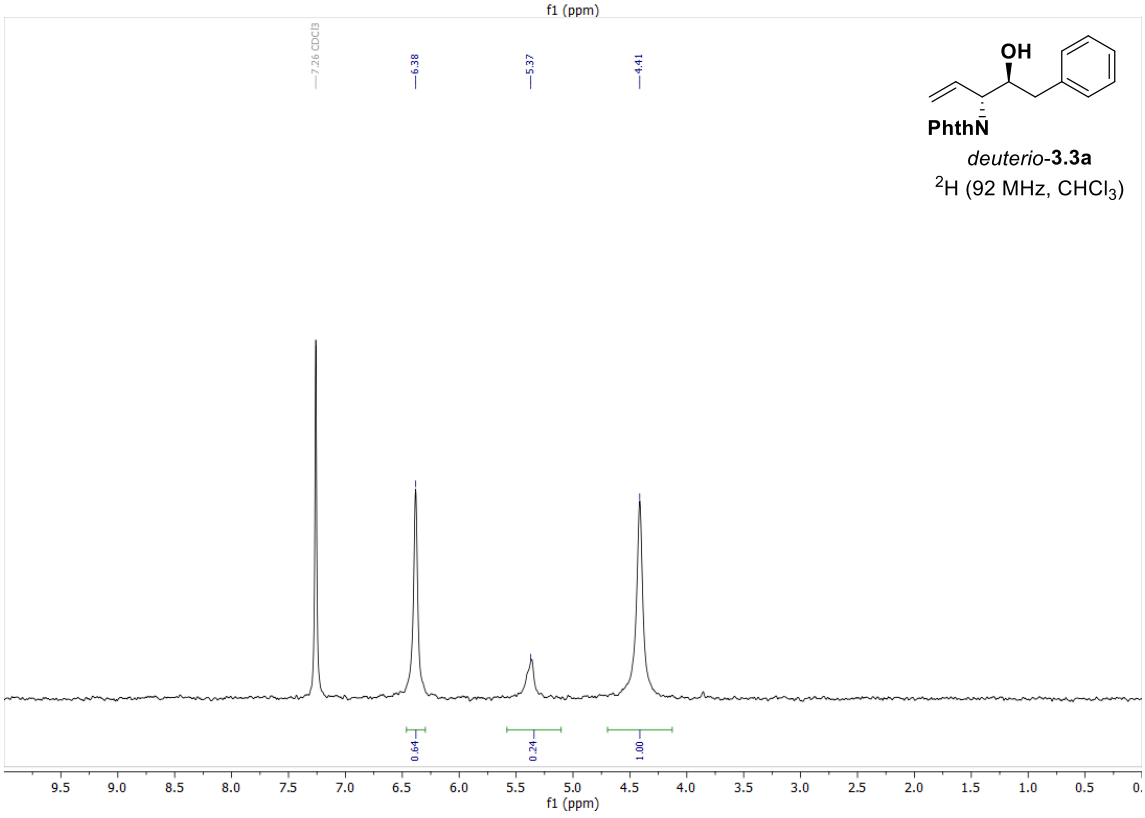
TLC (SiO_2) R_f = 0.35 (20:80 EtOAc:hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.28 – 7.15 (m, 5H), 6.39 – 6.30 (m, 0.4H), 5.37 – 5.28 (m, 1.75H), 4.78 – 4.76 (m, 1H), 3.42 (brs, 1H), 2.89 – 2.81 (m, 2H).

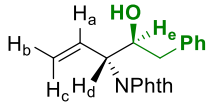
^{2}H NMR (92 MHz, $CHCl_3$) δ: 6.38 (brs, 0.6D), 5.37 (brs, 0.25D), 4.41 (brs, 1D).

HRMS (H+, *m/z*) for $C_{19}H_{15}D_2NO_3$: calcd. = 310.1407; found = 310.1416.


OH
PhthN
deuterio-3.3a
1H (500 MHz, CDCl3)
f1 (ppm)


OH
PhthN
deuterio-3.3a
2H (92 MHz, CHCl3)
f1 (ppm)

Competition experiment:



deuterio-**3.3a** and **3.3a**
$\mathbf{H_a}$ (5% ^{2}H), $\mathbf{H_b}$,$\mathbf{H_c}$ (<1% ^{2}H)
$\mathbf{H_d}$ (<1% ^{2}H), $\mathbf{H_e}$ (30% ^{2}H)

A mix of alcohol **3.2a** (120 µL, 1.0 mmol) and alcohol *deuterio*-**3.2a** (120.0 µL, 1.0 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), title compounds *deuterio*-**3.3a** and **3.3a** (31.9 mg, 0.10 mmol, >20:1 dr) was obtained as a light yellow solid in 52% yield.

TLC (SiO_2) R_f = 0.35 (20:80 EtOAc:hexanes)

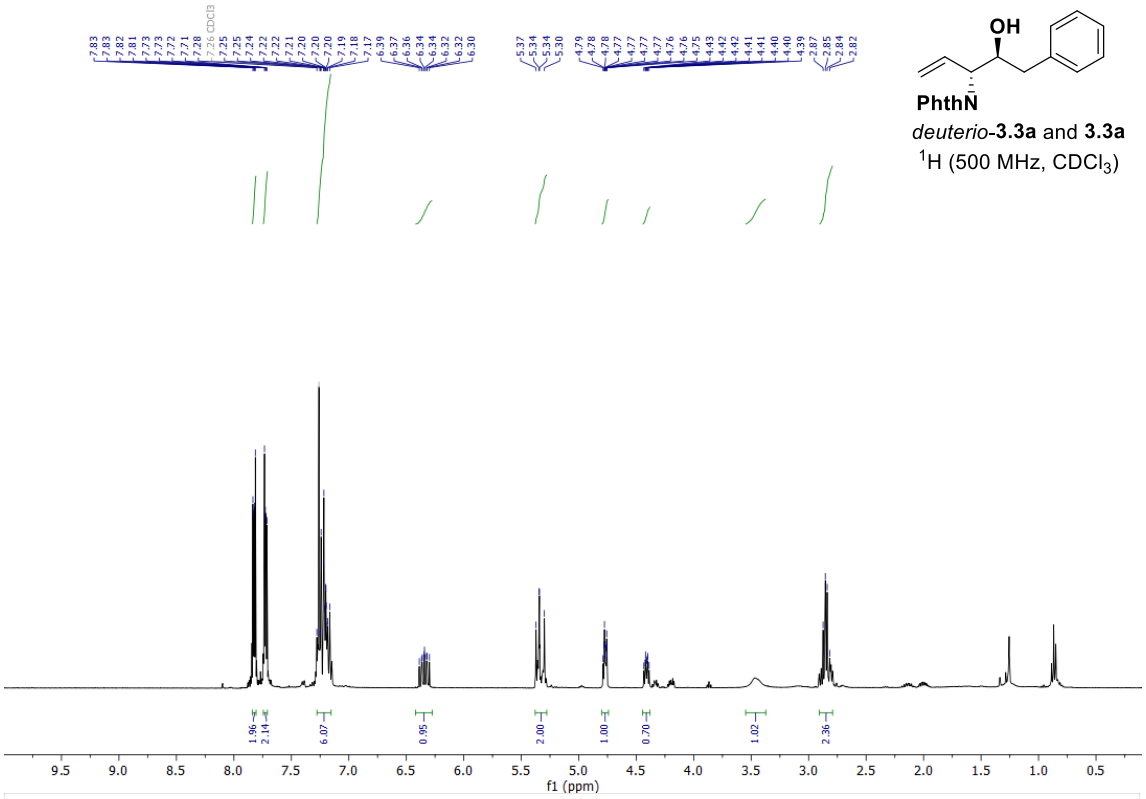
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.28 – 7.15 (m, 5H), 6.39 – 6.30 (m, 0.85H), 5.37 – 5.28 (m, 1.95H), 4.78 – 4.76 (m, 1H), 4.41 (ddd, *J* = 7.8, 5.9, 4.7 Hz, 0.7H), 3.42 (brs, 1H), 2.89 – 2.81 (m, 2H).

^{2}H NMR (92 MHz, $CHCl_3$) δ: 6.38 (brs, 1D), 5.37 (brs, 1D), 4.41 (brs, 1D).

HRMS (Na+, *m/z*) for $C_{19}H_{17}NO_3$: calcd. = 330.1101; found = 330.1105.

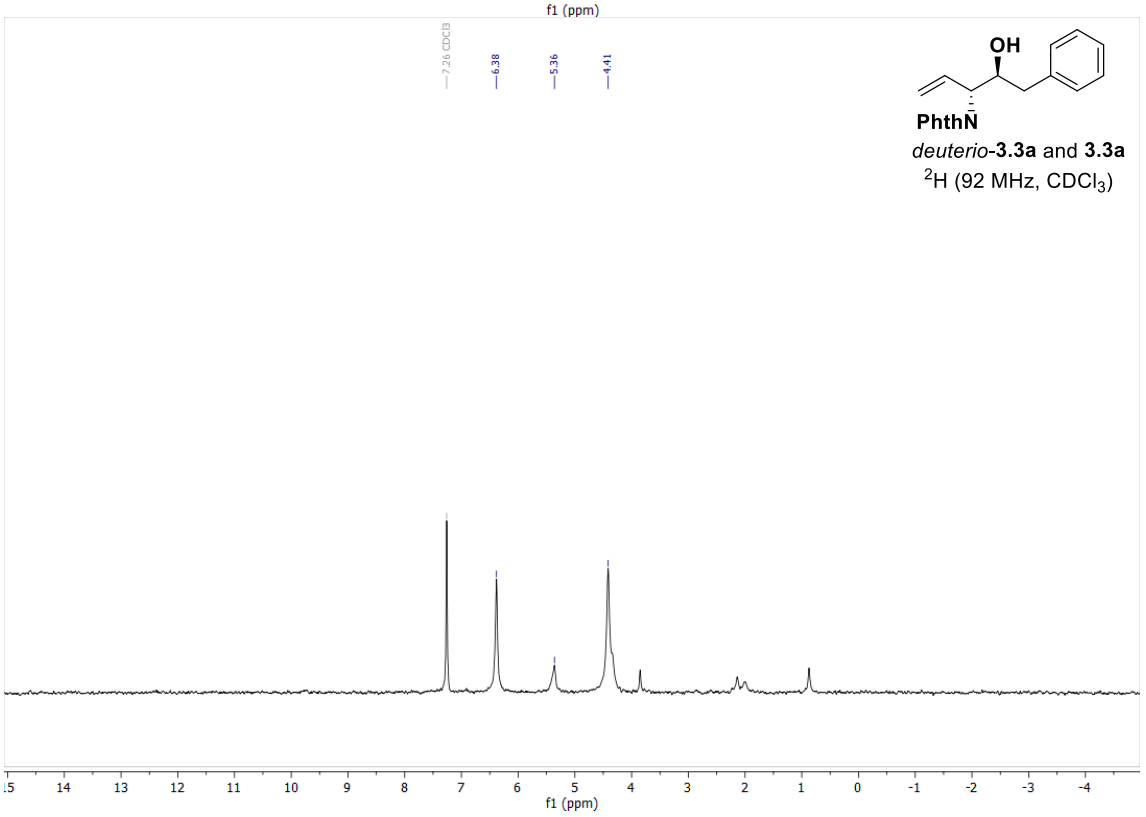
HRMS (Na+, *m/z*) for $C_{19}H_{16}DNO_3$: calcd. = 331.1163; found = 331.1164.

HRMS (Na+, *m/z*) for $C_{19}H_{15}D_2NO_3$: calcd. = 332.1226; found = 332.1226.



deuterio-**3.3a** and **3.3a**

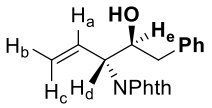
^{1}H (500 MHz, $CDCl_3$)



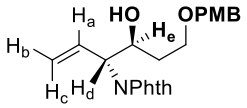
deuterio-**3.3a** and **3.3a**

^{2}H (92 MHz, $CDCl_3$)

Intermolecular competition experiment:



deuterio-**3.3a**
$\mathbf{H_a}$ (61% ^{2}H), $\mathbf{H_b}$,$\mathbf{H_c}$ (19% ^{2}H)
$\mathbf{H_d}$ (<1% ^{2}H), $\mathbf{H_e}$ (>99% ^{2}H)



deuterio-**3.3l**
$\mathbf{H_a}$ (64% ^{2}H), $\mathbf{H_b}$,$\mathbf{H_c}$ (19% ^{2}H)
$\mathbf{H_d}$ (<1% ^{2}H), $\mathbf{H_e}$ (<1% ^{2}H)

A mix of *dehydro*-**3.2l** (19 mg, 0.1 mmol) and Alcohol *deuterio*-**3.2a** (12 µL, 0.1 mmol) was subjected to standard reaction conditions (100 °C, 48 h). Upon flash column chromatography (SiO_2, 20:80 EtOAc:hexanes), title compounds *deuterio*-**3.3a** (13.0 mg, 0.042 mmol, 21% yield) and *deuterio*-**3.3l** (21.3 mg, 0.056 mmol, 28% yield) were obtained as a light yellow solid and pale yellow oil respectively.

TLC (SiO_2) $R_{f\text{-}deutreio\text{-}\mathbf{3a}}$ = 0.35 (20:80 EtOAc:hexanes)

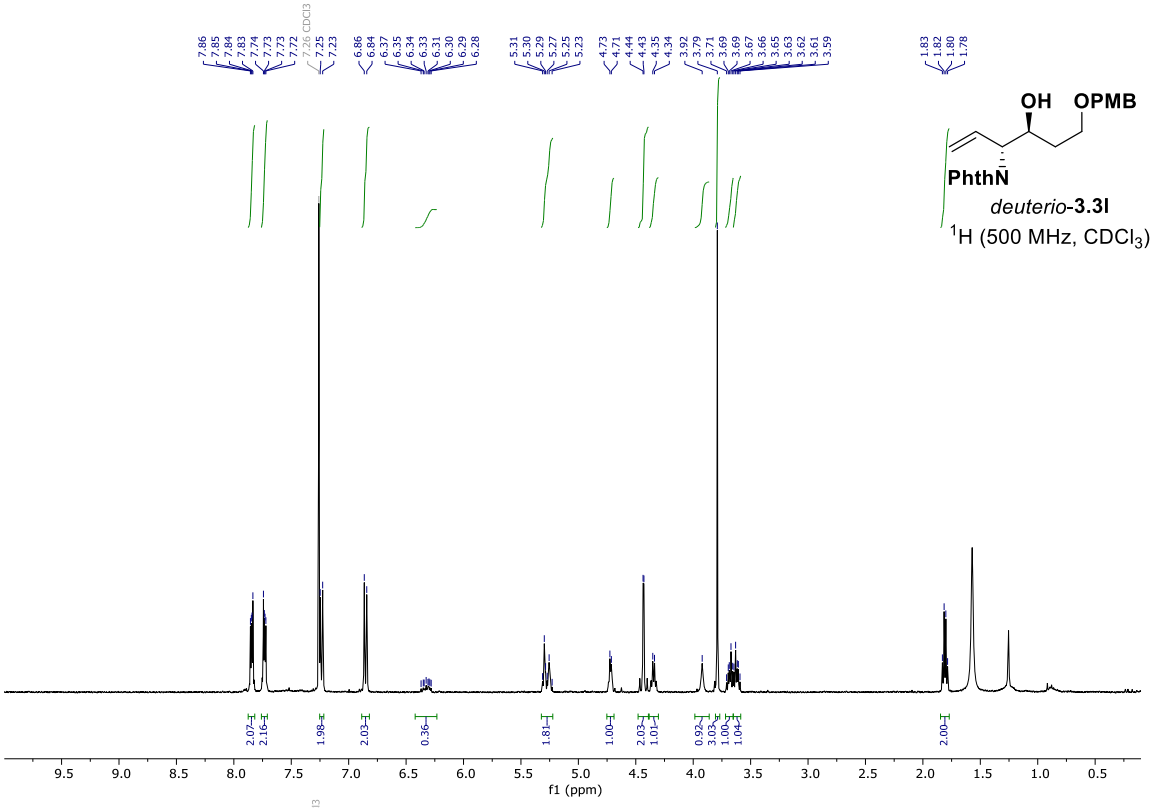
TLC (SiO_2) $R_{f\text{-}deuterio\text{-}\mathbf{3l}}$ = 0.28 (30:70 EtOAc:hexanes)

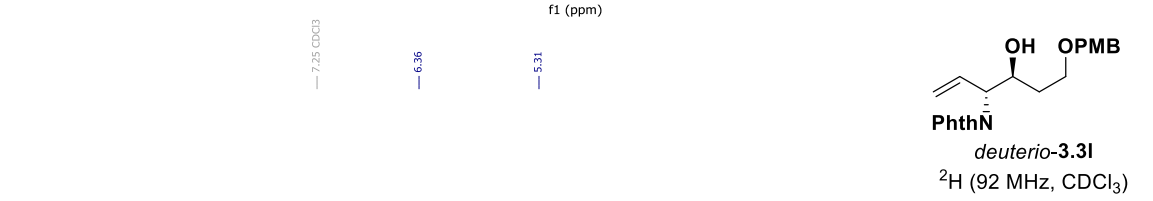
***Deuterio*-3l:**

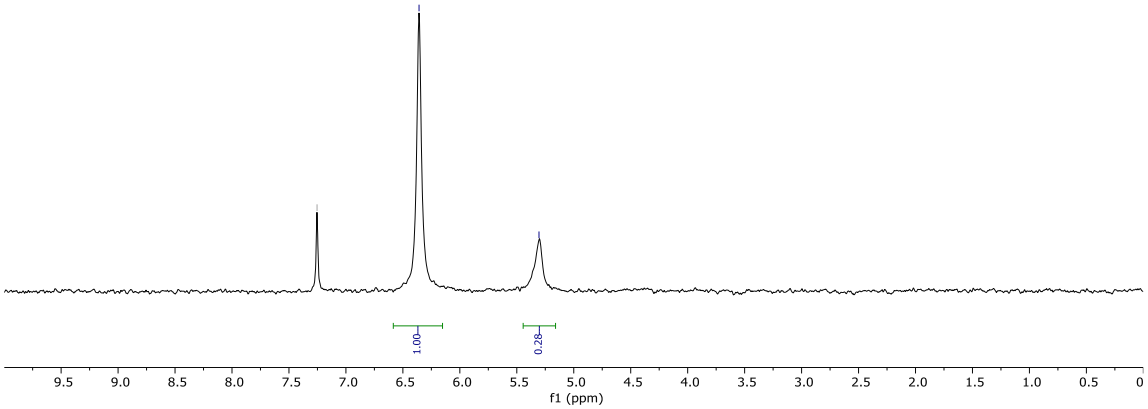
^{1}H NMR (500 MHz, CDCl3) δ: 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.38 – 6.28 (m, 0.4H), 5.32 – 5.23 (m, 1.90H), 4.74 – 4.69 (m, 1H), 4.46 – 4.39 (m, 2H), 4.35 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.92 (s, 1H), 3.78 (s, 3H), 3.71 – 3.65 (m, 1H), 3.64 – 3.58 (m, 1H), 1.85 – 1.77 (m, 2H).

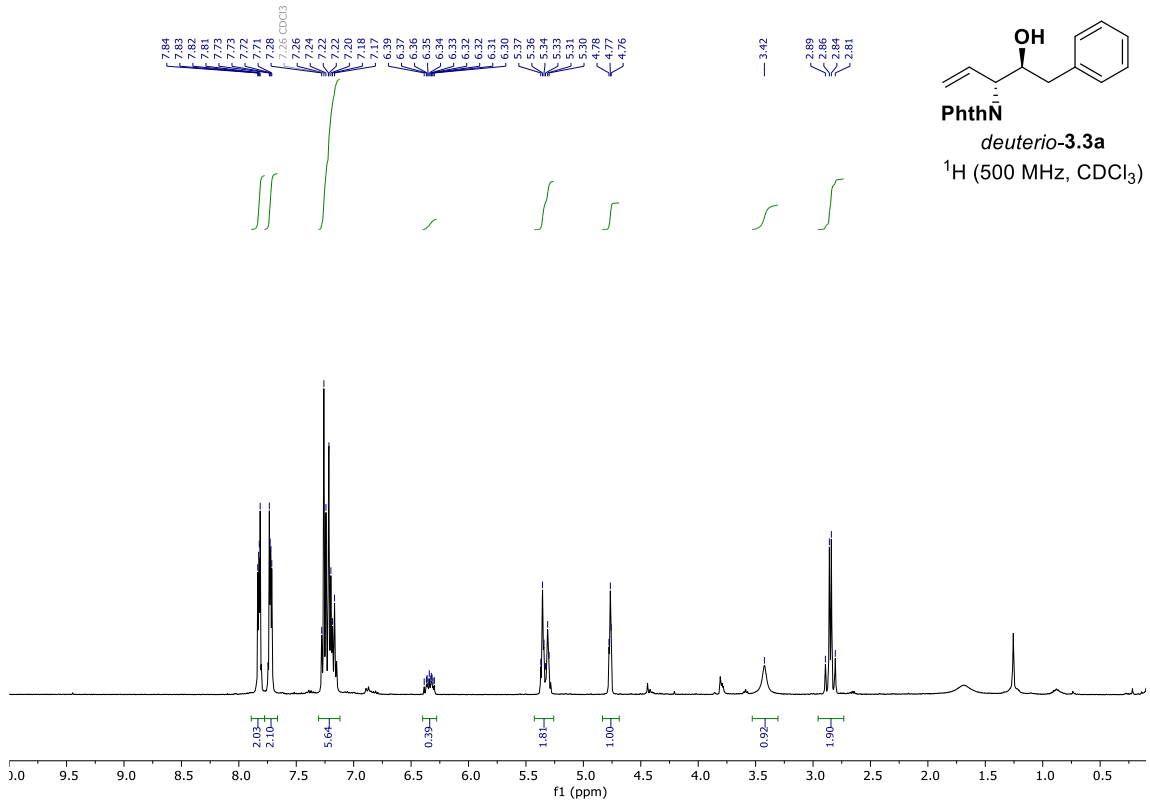
^{2}H NMR (92 MHz, $CHCl_3$) δ: 6.36 (brs, 1D), 5.31 (brs, 1D)

HRMS (Na+, *m/z*) for $C_{22}H_{22}DNO_5$: calcd. = 405.1531; found = 405.1530.


OH
OPMB
PhthN
deuterio-3.3l
1H (500 MHz, CDCl3)
f1 (ppm)


OH
OPMB
PhthN
deuterio-3.3l
2H (92 MHz, CDCl3)


f1 (ppm)

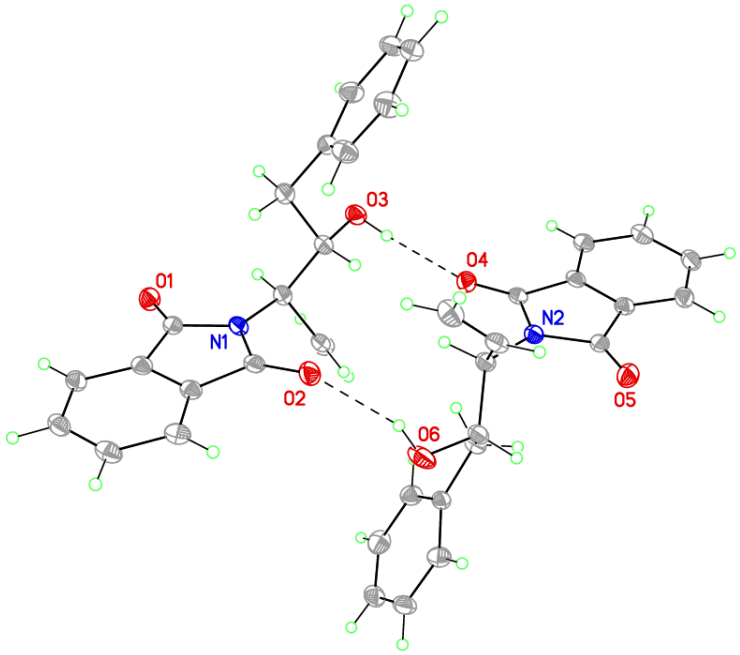

7.84
7.83
7.82
7.81
7.73
7.73
7.72
7.71
7.28
7.26 CDCl3
7.26
7.24
7.22
7.22
7.20
7.18
7.17
6.39
6.37
6.36
6.35
6.34
6.33
6.32
6.32
6.31
6.30
5.37
5.36
5.34
5.33
5.31
5.30
4.78
4.77
4.76
3.42
2.89
2.86
2.84
2.81
OH
PhthN
deuterio-3.3a
1H (500 MHz, CDCl3)
2.03
2.10
5.64
0.39
1.81
1.00
0.92
1.90
f1 (ppm)

3.5.3.7 Single Crystal Diffraction Data

Single Crystal Diffraction Data for Coupling Product 3.3a

Empirical formula	C19 H17 N O3	
Formula weight	307.33	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	triclinic	
Space group	P 1	
Unit cell dimensions	a = 7.6636(2) Å	α= 86.249(2)°.
	b = 9.5929(2) Å	β= 76.166(2)°.
	c = 10.8499(2) Å	γ = 79.110(2)°.
Volume	760.39(3) $Å^3$	
Z	2	
Density (calculated)	1.342 Mg/m^3	
Absorption coefficient	0.738 mm^{-1}	
F(000)	324	
Crystal size	0.34 x 0.12 x 0.065 mm^3	
Theta range for data collection	4.197 to 75.699°.	
Index ranges	-9<=h<=9, -11<=k<=12, -13<=l<=13	
Reflections collected	26510	
Independent reflections	5735 [R(int) = 0.0395]	
Completeness to theta = 67.684°	99.7 %	
Absorption correction	Gaussian and multi-scan	
Max. and min. transmission	1.00 and 0.534	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5735 / 3 / 433	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0357, wR2 = 0.0952	
R indices (all data)	R1 = 0.0367, wR2 = 0.0961	
Absolute structure parameter	0.04(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.175 and -0.218 $e.Å^{-3}$	

Figure 3.4 Crystal Structure of **3.3a** Dimer

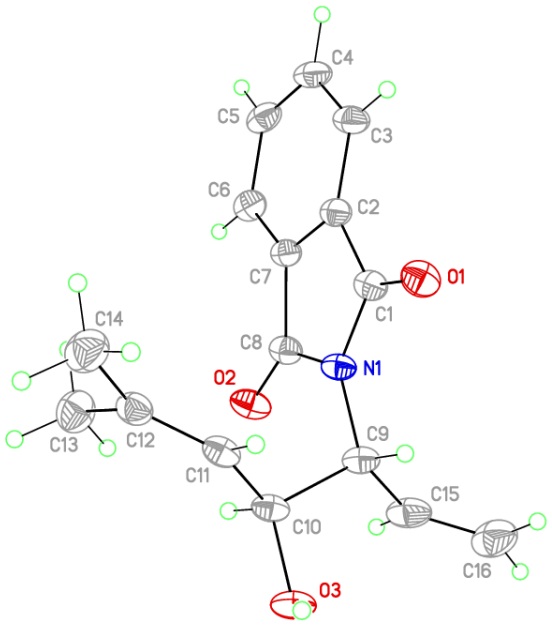


View of H-bound dimer formed in **3.3a** showing the heteroatom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Dashed lines are indicative of an H-bonding interaction.

Single Crystal Diffraction Data for Coupling Product 3.3v

Empirical formula	C16 H17 N O3	
Formula weight	271.30	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.3815(2) Å	α= 90°.
	b = 22.4250(2) Å	β= 117.675(2)°.
	c = 8.6781(2) Å	γ = 90°.
Volume	1444.49(5) $Å^3$	
Z	4	
Density (calculated)	1.248 Mg/m^3	
Absorption coefficient	0.702 mm^{-1}	
F(000)	576	
Crystal size	0.31 x 0.18 x 0.11 mm^3	
Theta range for data collection	3.943 to 76.170°.	
Index ranges	-10<=h<=10, -28<=k<=28, -10<=l<=10	
Reflections collected	33708	
Independent reflections	5984 [R(int) = 0.0393]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Gaussian and multi-scan	
Max. and min. transmission	1.00 and 0.713	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5984 / 1 / 389	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.1006	
R indices (all data)	R1 = 0.0378, wR2 = 0.1026	
Absolute structure parameter	-0.09(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.385 and -0.211 $e.Å^{-3}$	

Figure 3.5 Crystal Structure of **3.3v**

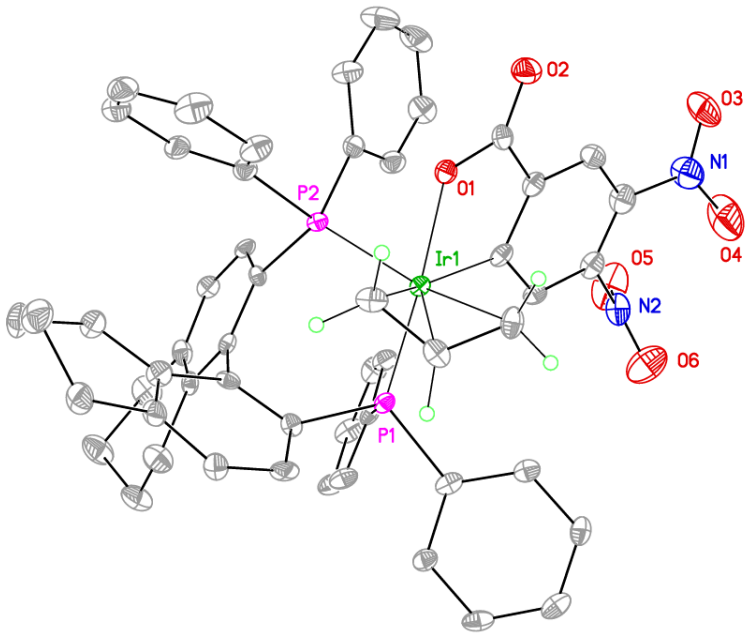


View of **3.3v** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Single Crystal Diffraction Data for (*R*)-Ir-VI

Empirical formula	C58 H55 Ir N2 O7 P2	
Formula weight	1146.18	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 14.339(2) Å	α= 90°.
	b = 17.764(2) Å	β= 90°.
	c = 18.920(3) Å	γ = 90°.
Volume	4819.4(11) $Å^3$	
Z	4	
Density (calculated)	1.580 Mg/m^3	
Absorption coefficient	2.896 mm^{-1}	
F(000)	2320	
Crystal size	0.220 x 0.110 x 0.100 mm^3	
Theta range for data collection	2.293 to 28.413°.	
Index ranges	-19<=h<=19, -23<=k<=23, -25<=l<=25	
Reflections collected	67534	
Independent reflections	12021 [R(int) = 0.0906]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	1.00 and 0.759	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12021 / 420 / 631	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0773	
R indices (all data)	R1 = 0.0489, wR2 = 0.0806	
Absolute structure parameter	-0.007(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.197 and -0.918 e.$Å^{-3}$	

Figure 3.6 Crystal Structure of (*R*)-Ir-**IV** Complex



View of the Ir complex showing the heteroatom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been omitted for clarity.

3.5.3.8 Kinetic Studies

Standard Conditions: To a dried 5 mL volumetric flask under an argon atmosphere charged with with (*R*)-Ir-**VI** (53.7mg, 0.05 mmol, 5 mol%), phthalimido-allene (277.8 mg, 1.5 mmol, 150 mol%), KH_2PO_4 (136.1 mg, 1 mmol, 100 mol%), and 1,3,5-trimethoxybenzene (internal standard, 168.2 mg , 1 mmol, 100 mol%) was added 2-phenylethanol (120 μL, 1 mmol, 100 mol%). The flask was then filled to the mark with dioxane and sonicated until full dissolution. The reaction mixture was then transfer *via* syringe to a condenser-tube sealed with a rubber septa under an argon atmosphere. The reaction mixture was then heated to 100 °C.

Reaction progress was monitored by sampling followed by NMR analysis. The reaction was sampled by removable of approximately 100 μL of the reaction mixture *via* syringe and dilution with $CDCl_3$.

Table 3.3 Further Reaction Conditions for the Kinetic Experiments

Experiment	[Ir] (M)	[3.1] (M)	[3.2a] (M)	[excess] [3.1]-[3.2a] (M)	Note
Standard	0.01	0.3	0.2	0.1	-
Different Excess 1	0.01	0.6	0.2	0.4	-
Different Excess 2	0.01	0.3	0.4	-0.1	-
Same Excess	0.01	0.2	0.1	0.1	-
Same Excess product addition	0.01	0.2	0.1	0.1	**3.3a** 0.08 M
Increased Catalyst	0.02	0.3	0.2	0.1	-
Added Aldehyde	0.01	0.3	0.2	0.1	*dehydro*-**3.2a** 0.01 M

Figure 3.7 Product Formation Under Standard Conditions

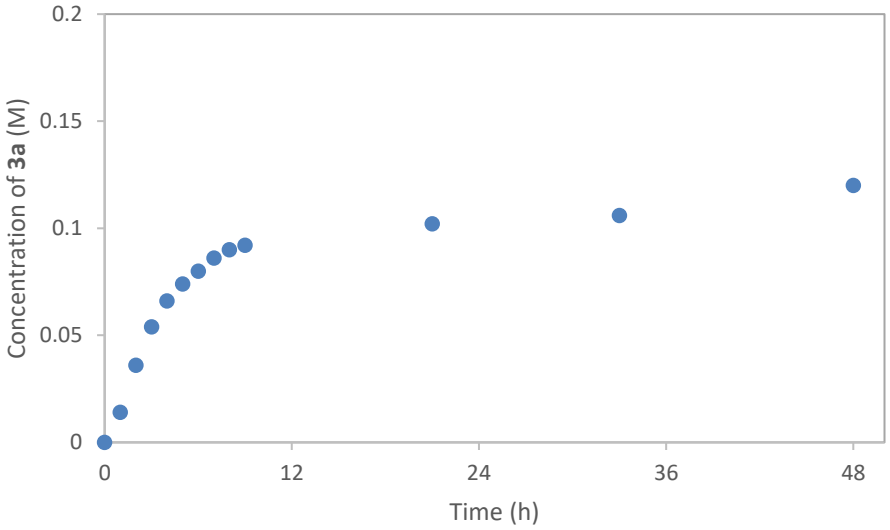


Figure 3.8 Product Formation Under Standard Conditions for First 2 Hours to Determine Initial Rate

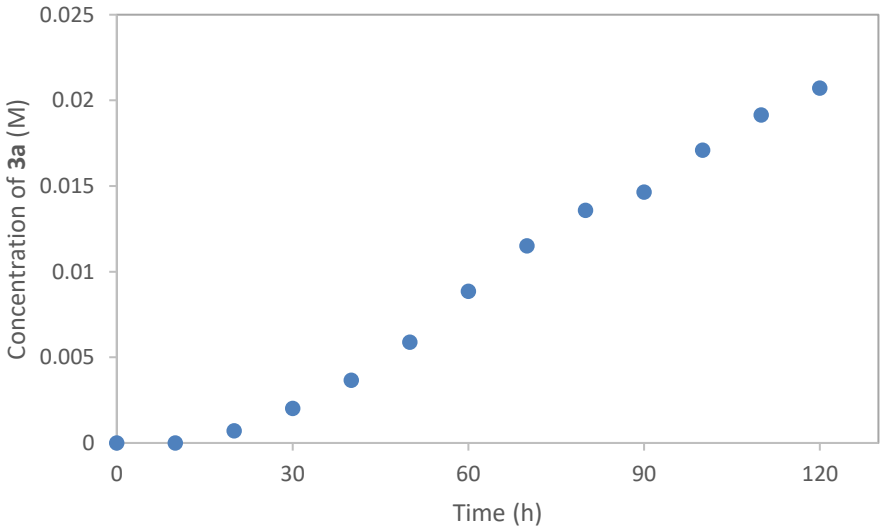


Figure 3.9 Product Formation Under Standard Conditions for First 2 Hours to Determine Initial Rate Utilizing *deuterio*-**3.2a**

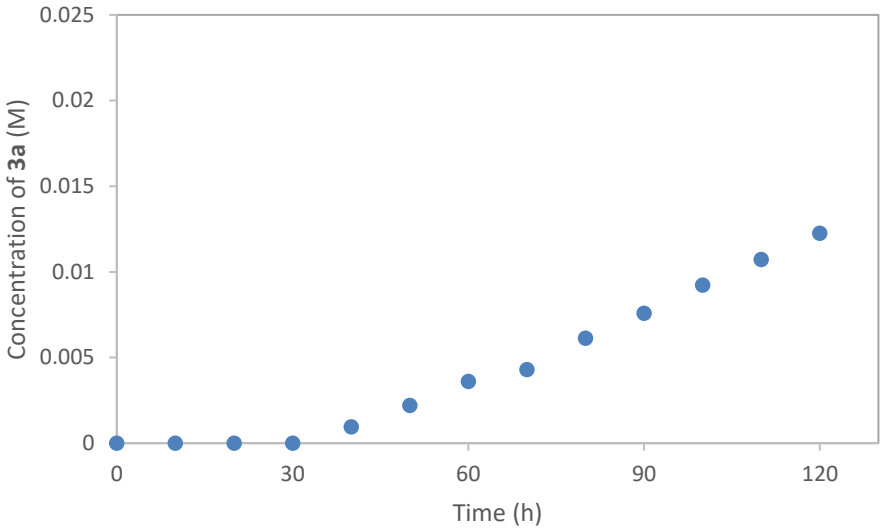


Figure 3.10 Product Formation Under Different Excess 1 Conditions

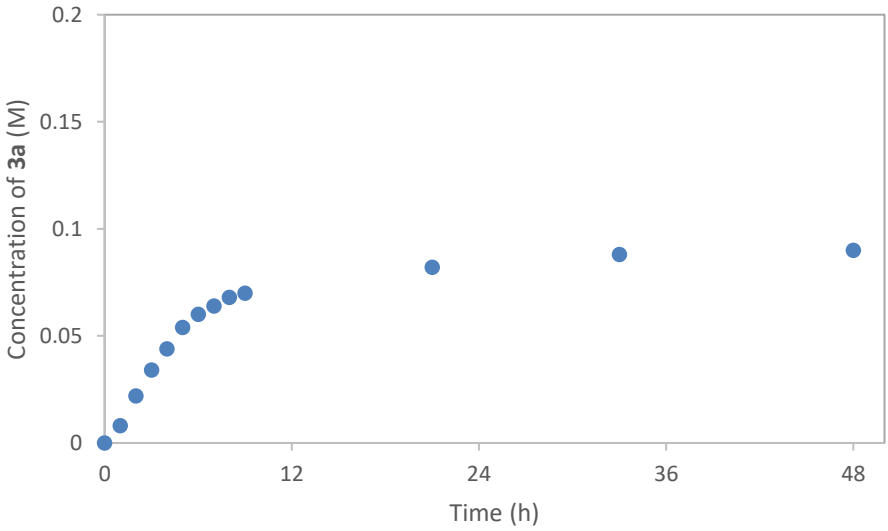


Figure 3.11 Product Formation Under Different Excess 2 Conditions

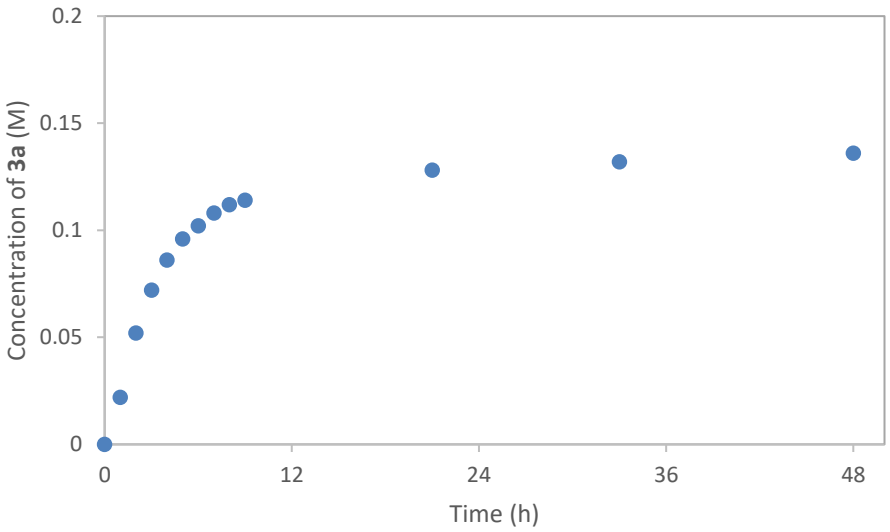


Figure 3.12 Product Formation Under Same Excess Conditions

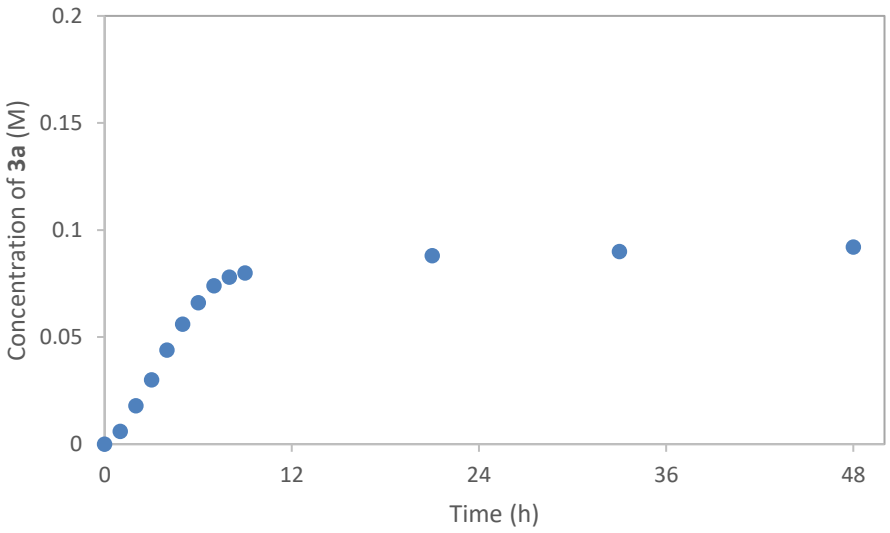


Figure 3.13 Product Formation Under Same Excess Conditions with Product Addition

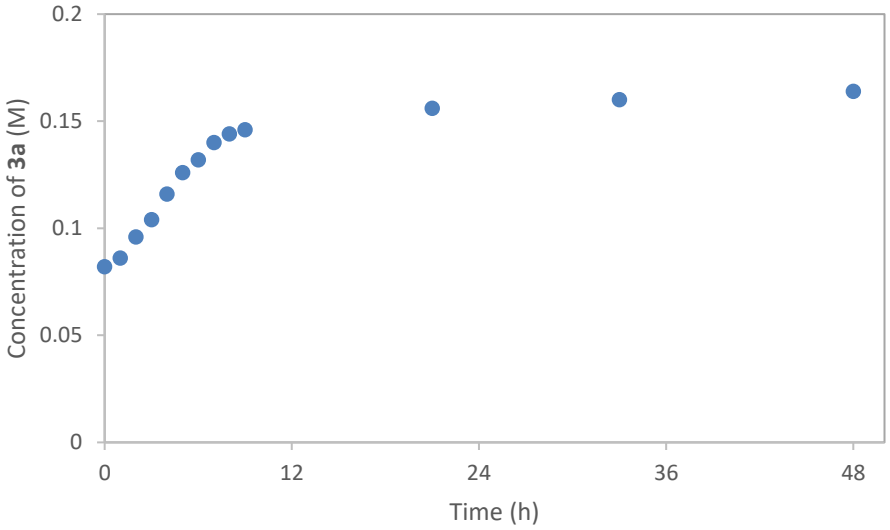


Figure 3.14 Product Formation Under Increased Catalyst Conditions

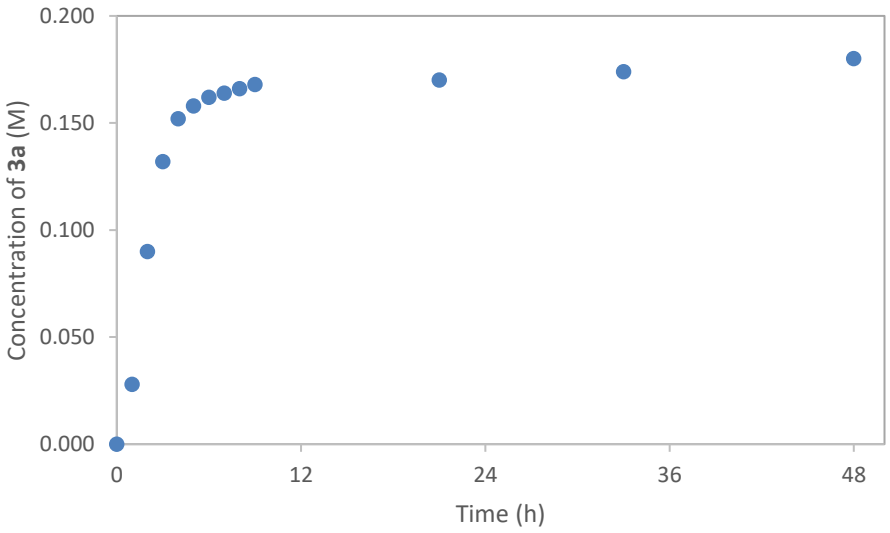


Figure 3.15 Product Formation Under Standard Conditions with 10 mol% Aldehyde *dehydro*-**3.2a** Added

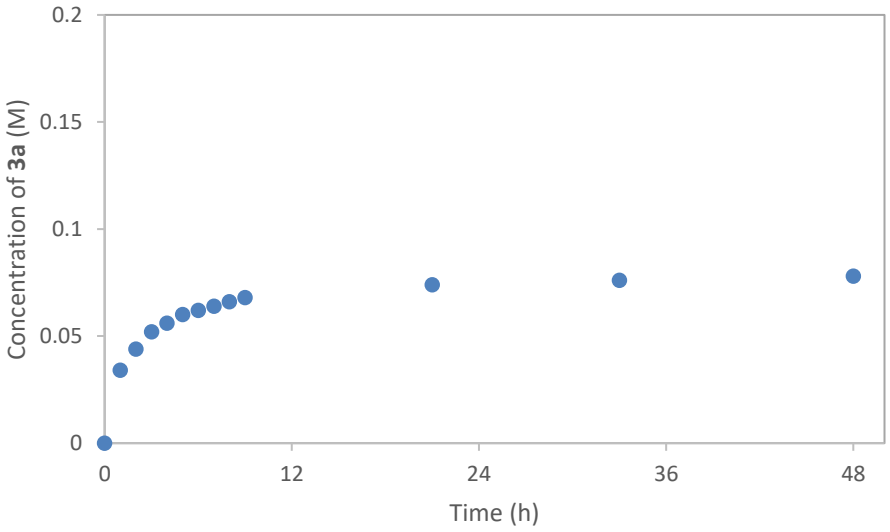
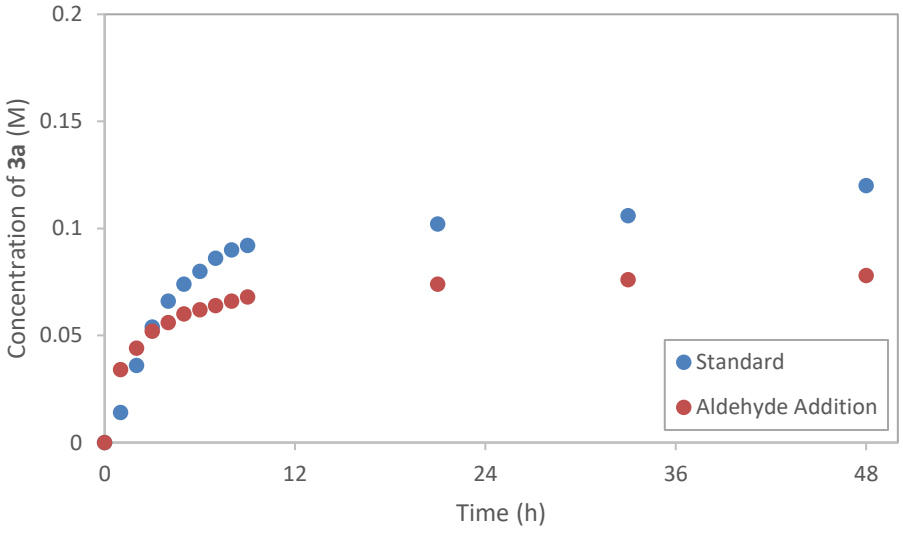
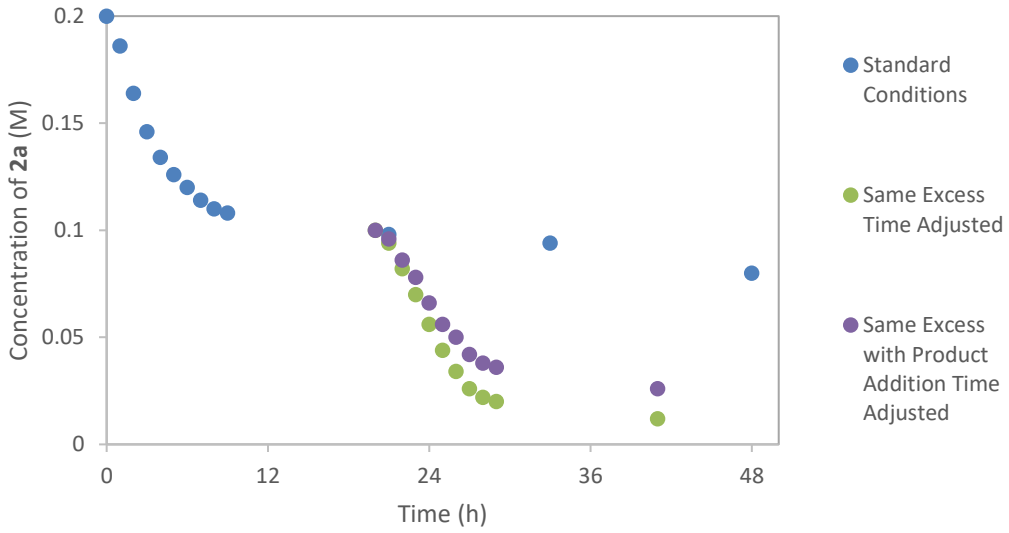


Figure 3.16 Product Formation Under Standard Conditions with 10 mol% Aldehyde *dehydro*-**3.2a** Added with Comparison to Standard Conditions – Negative Order



In order to determine if any catalyst deactivation occurred during the reaction the same excess protocol was utilized. The collected product concentration data for both the standard and same excess data sets were converted to alcohol concentration data ($[\mathbf{3.2a}]_t = [\mathbf{3.2a}]_0 - [\mathbf{3.3a}]_t$). Since the starting concentration of the same excess experiments is different than that of the standard experiment, the same excess time data was adjusted accordingly. This method is representative of starting the reaction from two different starting points. At the point where the standard data set reaches the starting point of the same excess data set they then represent a reaction with the same conditions, with the exception of the first containing product already present and a catalyst that has completed more turnovers.[20] The failure of these two curves to overlap indicates that significant catalyst deactivation occurs. Additionally, in the case of the same excess conditions with product addition, a slight shift towards the standard conditions indicates that the product is contributing to the deactivation pathway. This is only a moderate contribution.

Figure 3.17 Evaluation of Catalyst Performance Utilizing Same Excess Protocol



Chapter 4: Regio- and Enantioselective Iridium-Catalyzed Amination of Racemic Branched Alkyl-Substituted Allylic Acetates with Primary and Secondary Aromatic and Heteroaromatic Amines*

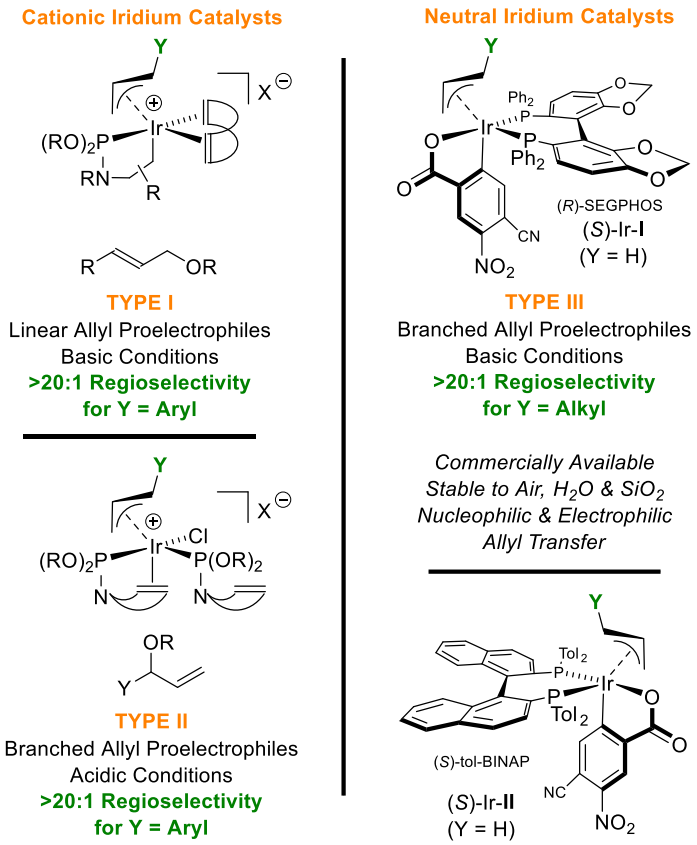
4.1 INTRODUCTION

Cyclometalated π-allyliridium C,O-benzoate complexes have been shown to catalyze diverse alcohol-mediated carbonyl allylations using allyl carboxylates as pronucleophiles.[1] In these umpoled allylations,[2] the *C,O*-benzoate moiety assists in maintaining neutrality and, hence, nucleophilicity of the π-allyliridium intermediate. Nucleophilic properties are displayed by other neutral π-allyliridium species.[3] In contrast, as illustrated by enantioselective Tsuji−Trost-type allylic aminations developed by Takeuchi,[4,5] Helmchen,[6,7] Hartwig,[8,9] Carreira,[10] and You,[11,12] cationic π-allyliridium species invariably serve as electrophiles. In this latter context, two distinct classes of iridium catalysts have emerged. Type I catalysts are used under basic conditions in combination with linear allyl pro-electrophiles (as branched allyl proelectrophiles react stereospecifically).[13] Type II catalysts are used under acidic conditions in combination with branched allyl proelectrophiles, which react in a non-stereospecific fashion, perhaps due to displacement of the π-bond of (σ+π)-allyl (enyl) iridium intermediates by the tethered olefin of the phosphoramidite ligand (Figure 4.1).[14]

The Krische group previously discovered that neutral π-allyliridium *C,O*-benzoate complexes, which behave as nucleophilic allyl donors,[1] can also act as electrophiles, representing the first examples of amphiphilic reactivity in the context of transition metal

* This chapter is based on the previously published work:
Kim, S. W.; Schwartz, L. A.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed Amination of Racemic Branched Alkyl-Substituted Allylic Acetates with Primary and Secondary Aromatic and Heteroaromatic Amines. *J. Am. Chem. Soc.* **2019**, *141*, 671.
L.A.S. contributed to reaction optimization (Scheme 4.1), substrate scope (Tables 4.1, 4.2, and 4.3; Scheme 4.2), and preparation of manuscript and supporting information.

Figure 4.1 Cationic versus Neutral Chiral Iridium Complex for Regio- and Enantioselective Allylic Amination



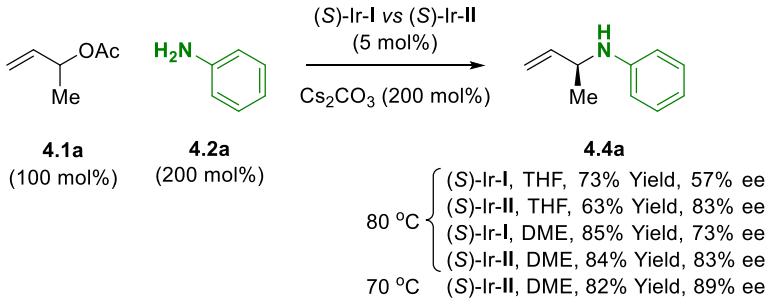
catalysis.[15] In the initial communication of these findings, enantioselective allylic aminations of branched allylic acetates bearing linear alkyl groups with primary aliphatic amines were disclosed.[15] These aminations proceed with complete branched regioselectivity, overcoming a significant limitation associated with Type I and II catalysts, which display incomplete regioselectivity for π-allyl precursors bearing linear alkyl groups.[16,17] With regard to the amine nucleophile, the Type III SEGPHOS-modified π-allyliridium complexes used in the initial study enforced high enantioselectivities in reactions of primary aliphatic amines (Figure 4.1). The corresponding tol-BINAP-modified iridium catalyst provides a significant expansion in scope, enabling highly enantioselective aminations of branched alkyl-substituted allylic acetates with electronically diverse

primary and secondary aryl amines, including site-selective reactions of bis(amine) nucleophiles. Additionally, deuterium labeling studies corroborate C–N bond formation occurs via an outer-sphere mechanism.

4.2 Reaction Development and Scope

To develop highly regio- and enantioselective allylic aminations mediated by aryl amines, a series of π-allyliridium *C,O*-benzoate complexes were evaluated in reactions of α-methyl allyl acetate (100 mol%) and aniline (200 mol%) under conditions previously optimized for primary aliphatic amines.[15] The iridium catalyst modified by tol-BINAP, (*S*)-Ir-**II**, delivered the product of allylic amination **4.4a** with significantly higher levels of enantioselectivity than the corresponding SEGPHOS-modified catalyst, (*S*)-Ir-**I**, but a lower isolated yield of **4.4a** was observed (Scheme 4.1). Changing the solvent from THF to DME improved the isolated yield of 4**.4a**, and by decreasing the reaction temperature from 80 to 70 °C **4.4a** could be formed in 82% yield and 89% enantiomeric excess (Scheme 4.1).

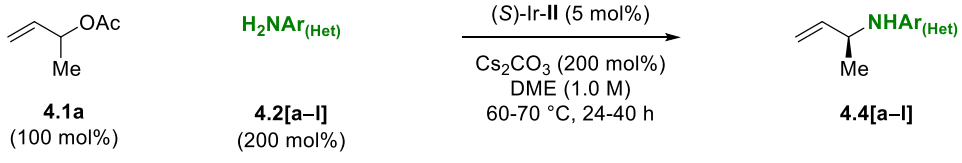
Scheme 4.1 Selected Optimization Experiments in the Iridium-Catalyzed Amination of α-Methyl Allyl Acetate **4.1a** with Aniline **4.4a**



Deviation from these reaction parameters did not result in further improvement, and given the low cost of tol-BINAP these conditions were adopted to explore the scope of primary aromatic and heteroaromatic amine nucleophiles **4.2[a–l]** in aminations of α-

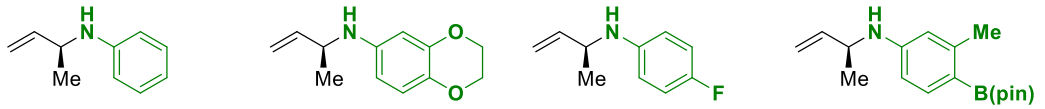
methyl allyl acetate (Table 4.1). Amine nucleophiles containing a diverse array of functional groups were examined to mirror challenges faced in medicinal chemistry. In each case, the targeted products of allylic amination **4.4[a−l]** were formed with complete

Table 4.1 Iridium-Catalyzed Amination of α-Methyl Allyl Acetate **4.1a** with Primary Aromatic and Heteroaromatic Amine **4.2[a–l]** To Form Enantiomerically Enriched Allylic Amines **4.4[a–l]**[a]



4.1a (100 mol%) | **4.2[a–l]** (200 mol%) | **4.4[a–l]**

4.2a, Ar = Ph	**4.2b**, Ar = 6-(benzodioxane)	**4.2c**, Ar = 4-F-Ph	**4.2d**, Ar = 3-Me-4-B(pin)-Ph
4.2e, Ar = 2-F-4-OMe-Ph	**4.2f**, Ar = 4-NMe_2-Ph	**4.2g**, Ar = 6-(*N*-Me-indazole)	**4.2h**, Ar = 5-(2-morph-pym)
4.2i, Ar = 7-(benzothiazole)	**4.2j**, Ar = 3-SO_2Me-Ph	**4.2k**, Ar = 2-(pyridine)	**4.2l**, Ar = 3-(pyridine)

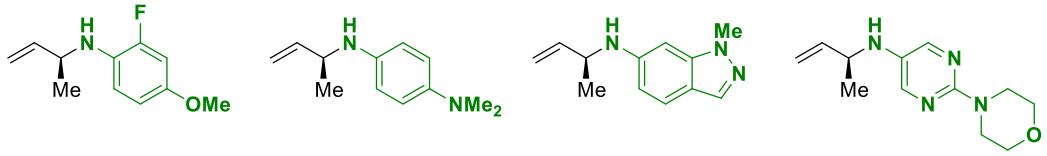


4.4a
82% Yield
>99:1 rr, 89% ee
$[\alpha]_D$ = -3.9
(c = 0.2, $CHCl_3$)

4.4b
85% Yield
>99:1 rr, 90% ee

4.4c
83% Yield
>99:1 rr, 90% ee

4.4d
78% Yield
>99:1 rr, 89% ee

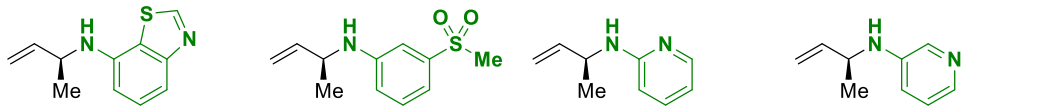


4.4e
79% Yield
>99:1 rr, 88% ee

4.4f
89% Yield
>99:1 rr, 90% ee

4.4g
81% Yield
>99:1 rr, 87% ee

4.4h
82% Yield
>99:1 rr, 89% ee



4.4i
82% Yield
>99:1 rr, 89% ee

4.4j
85% Yield
>99:1 rr, 90% ee

4.4k
83% Yield
>99:1 rr, 90% ee

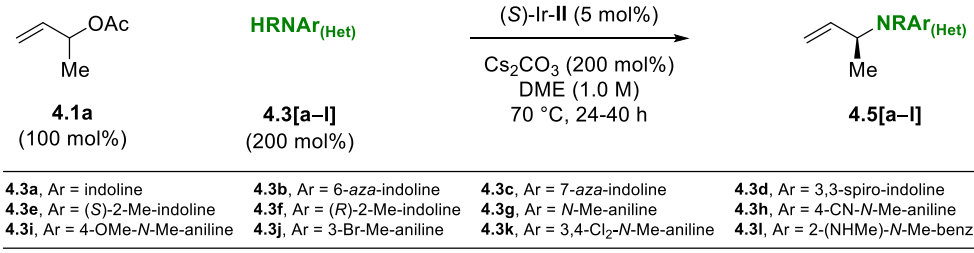
4.4l
78% Yield
>99:1 rr, 89% ee

[a]Yields of material isolated by silcia gel chromatography. Enantioselectivities were determined by chrial stationary-phase HPLC analysis.

branched regioselectivity and uniformly high levels of enantioselectivity. As illustrated in the formation of **4.4d**, which incorporates a pinacol boronate moiety, the reaction conditions tolerate rather sensitive functional groups. The tolerance of ortho-substituted anilines, as demonstrated by the formation of **4.4e**, is also noteworthy. Perhaps the most striking feature, however, is the compatibility of the catalyst with electronically diverse aryl amine partners and the tolerance of Lewis basic *N*-heterocycles, as illustrated by the formation **4.4k** and **4.4l**. The absolute stereochemical assignment of adducts **4.4[b−l]** is made in analogy to that determined for compound **4.4a**, which has been prepared in enantiomerically enriched form in two separate reports.[8d,18]

In a further exploration of scope, optimized conditions were applied to the amination of α-methyl allyl acetate **4.1a** using secondary aromatic and heteroaromatic amine nucleophiles **4.3[a−l]** (Table 4.2). Indoline **4.3a**, 6- and 7-aza-indolines **4.3b** and **4.3c**, and the 3,3′-spirocyclic indoline **4.3d** each underwent asymmetric allylation with complete branched regioselectivity and high levels of enantioselectivity. Pronounced match-mismatched effects were observed in the conversion of (*S*)- and (*R*)-2-methyl indolines **4.3e** and **4.3f** to adducts **4.5e** and **4.5f**, respectively, suggesting the potential for kinetic resolution. The amination of **4.1a** using *N*-methyl aniline **4.3g** and related compounds **4.3h** and **4.3i** bearing electron withdrawing and donating groups at the *para*-position proceeded smoothly to form adducts **4.5[g−i]**, respectively. Among these three *N*-methyl aniline derivatives (**4.3[g−i]**), amination using the more-electron-rich *N*-methyl-*p*-anisidine **4.3i** occurred with notably higher levels of enantioselectivity. As illustrated by the formation of **4.5j** and **4.5k**, *N*-methyl anilines containing bromide (**4.3j**) and chloride (**4.3k**) functional groups are tolerated. Finally, amination of **4.1a** using *N*-methyl-2-(methylamino)benzimidazole **4.3l** is remarkably efficient, providing adduct **4.5l** in 94% yield with complete selectivity for allylation of the extranuclear 2-(methylamino) moiety.

Table 4.2 Iridium-Catalyzed Amination of α-Methyl Allyl Acetate **4.1a** with Secondary Aromatic and Heteroaromatic Amines **4.3[a–l]** To Form Enantiomerically Enriched Allylic Amines **4.5[a–l]**[a]

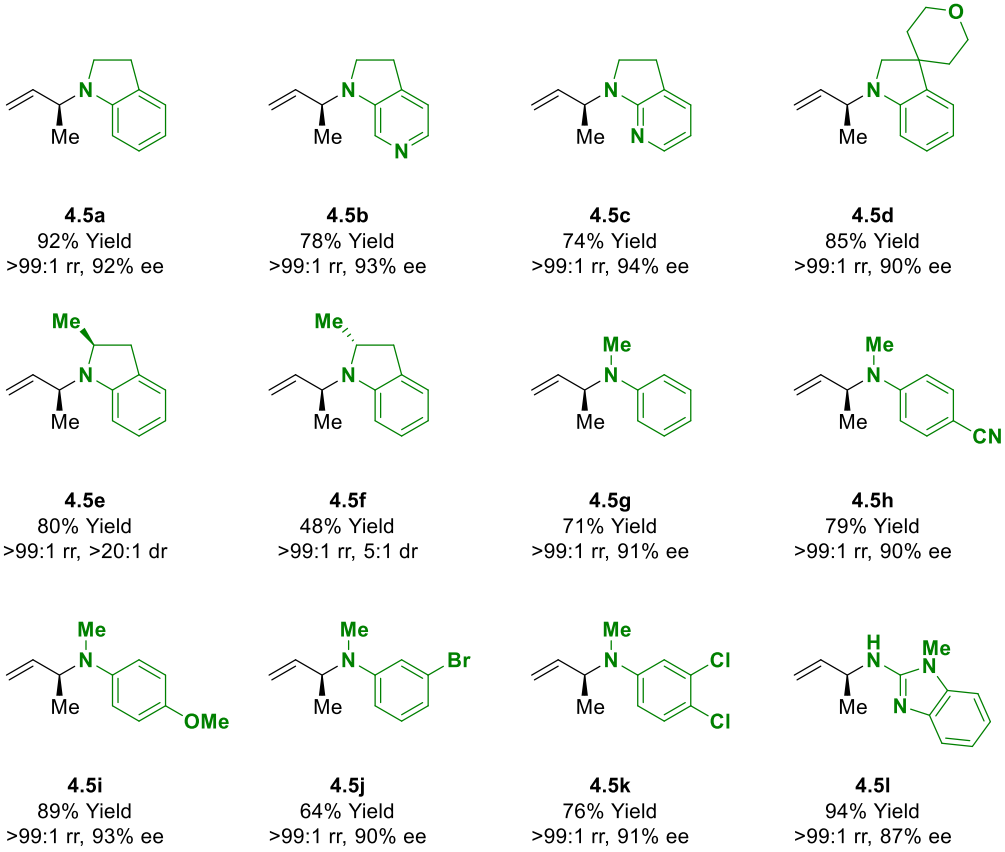


4.1a (100 mol%)

4.3[a–l] (200 mol%)

4.5[a–l]

4.3a, Ar = indoline; **4.3b**, Ar = 6-*aza*-indoline; **4.3c**, Ar = 7-*aza*-indoline; **4.3d**, Ar = 3,3-spiro-indoline
4.3e, Ar = (*S*)-2-Me-indoline; **4.3f**, Ar = (*R*)-2-Me-indoline; **4.3g**, Ar = *N*-Me-aniline; **4.3h**, Ar = 4-CN-*N*-Me-aniline
4.3i, Ar = 4-OMe-*N*-Me-aniline; **4.3j**, Ar = 3-Br-Me-aniline; **4.3k**, Ar = 3,4-Cl_2-*N*-Me-aniline; **4.3l**, Ar = 2-(NHMe)-*N*-Me-benzimidazole



4.5a
92% Yield
>99:1 rr, 92% ee

4.5b
78% Yield
>99:1 rr, 93% ee

4.5c
74% Yield
>99:1 rr, 94% ee

4.5d
85% Yield
>99:1 rr, 90% ee

4.5e
80% Yield
>99:1 rr, >20:1 dr

4.5f
48% Yield
>99:1 rr, 5:1 dr

4.5g
71% Yield
>99:1 rr, 91% ee

4.5h
79% Yield
>99:1 rr, 90% ee

4.5i
89% Yield
>99:1 rr, 93% ee

4.5j
64% Yield
>99:1 rr, 90% ee

4.5k
76% Yield
>99:1 rr, 91% ee

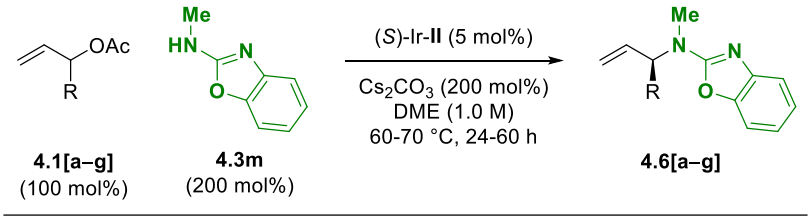
4.5l
94% Yield
>99:1 rr, 87% ee

[a]Yields of material isolated by silcia gel chromatography. Enantioselectivities were determined by chrial stationary-phase HPLC analysis.

To assess how structural variation of the π-allyliridium intermediate impacts reactivity, regio- and stereoselectivity, a set of branched allylic acetates **4.1[a−g]** were explored in aminations mediated by 2-(methylamino)benzoxazole **4.3m** (Table 4.3). In addition to α-methyl allyl acetate **4.1a**, linear alkyl-substituted allylic acetates **4.1b** and**4.1c**

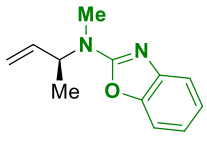
smoothly underwent amination to form adducts **4.6[a−c]** as single regioisomers with high levels of enantiomeric enrichment. Allylic acetates **4.1[d−f]**, which incorporate cycloalkyl

Table 4.3 Iridium-Catalyzed Amination of α-Substituted Allyl Acetates **4.1[a–g]** with Secondary Heteroaromatic Amine **4.3m** To Form Enantiomerically Enriched Allylic Amines **4.6[a–g]**[a]

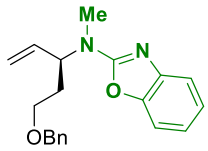


4.1[a–g] (100 mol%) **4.3m** (200 mol%) **4.6[a–g]**

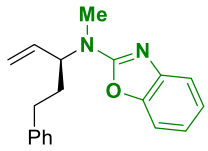
4.1a, R = Me	**4.1b**, R = CH_2CH_2OBn	**4.1c**, R = CH_2CH_2Ph
4.1d, R = cyclopropyl	**4.1e**, R = cyclobutyl	**4.1f**, R = cyclopentyl
4.2g, R = (*S*)-citronellol acetate		



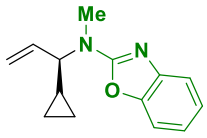
4.6a
95% Yield
>99:1 rr, 91% ee



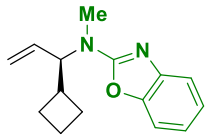
4.6b
93% Yield
>99:1 rr, 92% ee



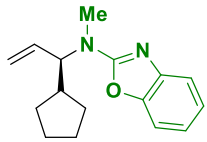
4.6c
92% Yield
>99:1 rr, 92% ee



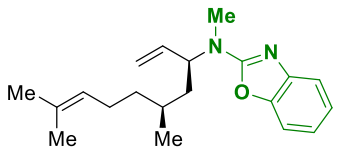
4.6d
81% Yield
>99:1 rr, 90% ee



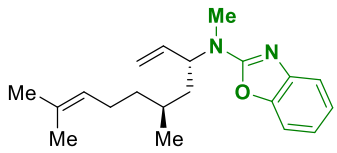
4.6e
71% Yield
>99:1 rr, 90% ee



4.6f
81% Yield
>99:1 rr, 85% ee



4.6g
80% Yield
>99:1 rr, 10:1 dr, (*S*)-Ir-**II**



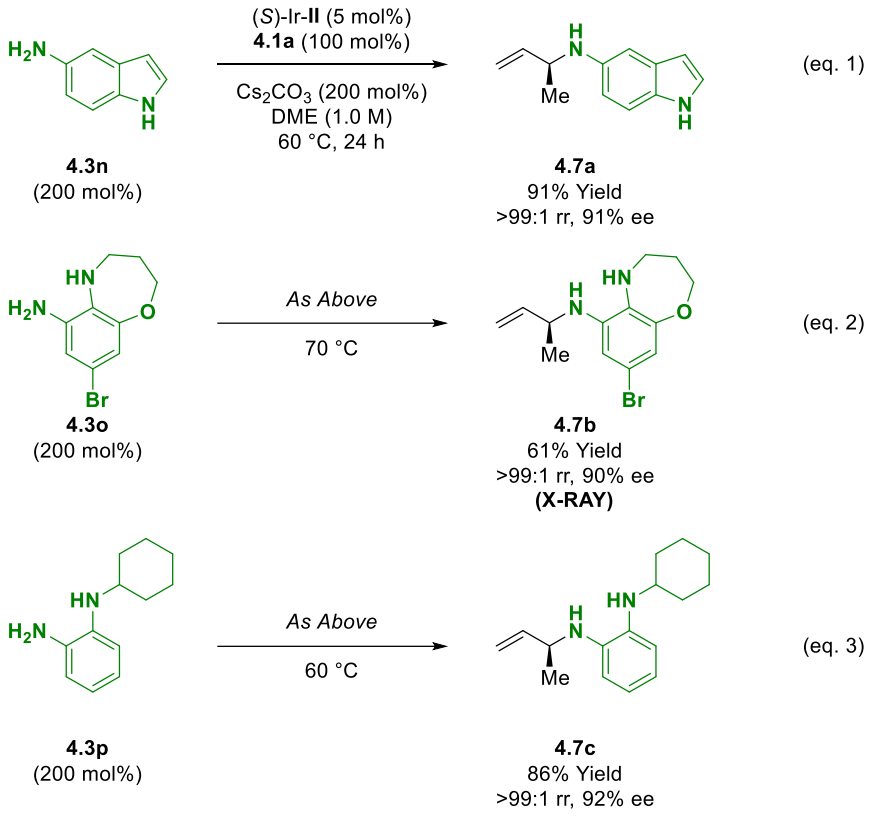
iso-**4.6g**
76% Yield
>99:1 rr, 20:1 dr, (*R*)-Ir-**II**

[a]Yields of material isolated by silcia gel chromatography. Enantioselectivities were determined by chrial stationary-phase HPLC analysis.

substituents, delivered adducts **4.6[d−f]** as single regioisomers, although an erosion in enantioselectivity is observed using the larger cyclopentyl-substituted allyl acetate **4.1f**. Finally, using the enantiomeric iridium catalysts (*S*)-Ir-**II** and (*R*)-Ir-**II**, the (*S*)-citronellol-derived allylic acetate **4.1g** reacts with **4.3m** to form **4.6g** and *iso*-**4.6g**, respectively, with good levels of catalyst-directed diastereoselectivity. Under these conditions, aryl-substituted allyl acetates gave low yields (<10%) of allylic amination product, and linear allylic acetates provided mixtures of allylic amination and hydroamination product in low isolated yield.[19]

Having established the ability to functionalize both primary and secondary aromatic amines, we attempted the site-selective modification of reactants **4.3[n−p]**, which incorporate both primary and secondary aromatic amines, using the branched allylic acetate **4.1a** (Scheme 4.2, eqs 1−3). Upon exposure to standard conditions, 5-aminoindole **4.3n** undergoes completely chemoselective functionalization at the primary amine to form adduct **4.7a** as a single constitutional isomer with excellent levels of enantioselectivity (Scheme 4.2, eq. 1). Similarly, in the conversion of **4.3o** to adduct **4.7b**, complete control of regio- and site-selectivity is accompanied by high levels of enantioselectivity (Scheme 4.2, eq. 2). The structure of adduct **4.7b** was verified by single crystal X-ray diffraction analysis, further corroborating the absolute stereochemical assignment of adducts **4.4[a−l]**, **4.5[a−l]** and **4.6[a−g]**. Finally, *N*-cyclohexyl-1,2-diaminobenzene **4.3p** reacts with **4.1a** to deliver adduct **4.7c**, which is modified exclusively at the primary amine (Scheme 4.2, eq. 3). The ability to engage diamines in site-selective regio- and enantioselectiveamination enhances step economy by avoiding manipulations devoted to *N*-protection–deprotection.

Scheme 4.2 Site-Selective Iridium-Catalyzed Amination of α-Methyl Allyl Acetate **4.1a** with Amines **4.3[n–p]** To Form Enantiomerically Enriched Allylic Amines **4.7[a–c]**

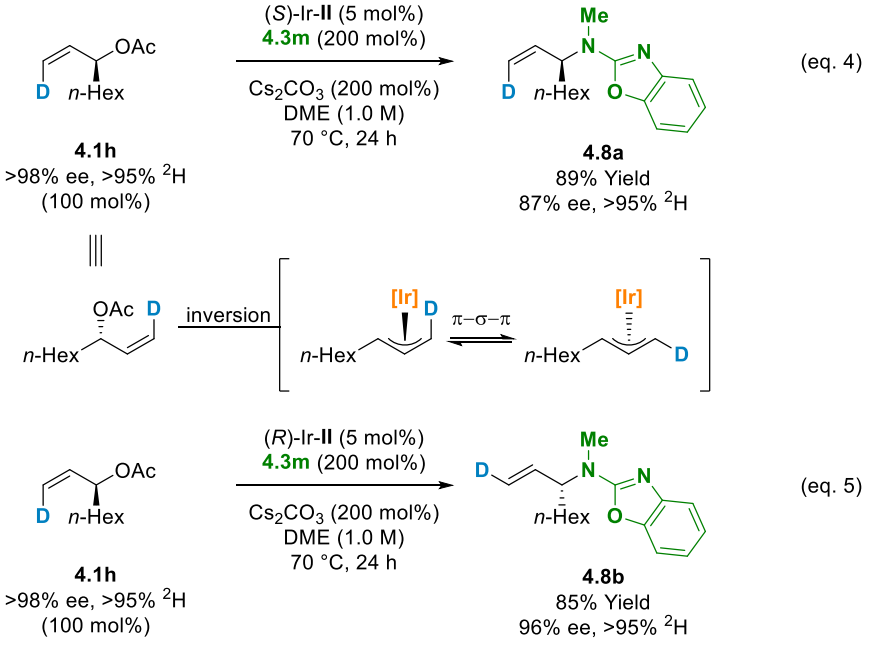


4.3 Mechanism and Discussion

To better understand the nature of the C–N bond forming event, asymmetric amination of the enantiomerically enriched (*Z*)-deuterated allylic acetate **4.1h** was conducted under standard conditions using (*S*)-Ir-**II** (Scheme 4.3, eq. 4).[20] Compound **4.8a** is formed with complete alkene (*Z*)-stereoselectivity, as determined by ^{1}H NMR. Assuming formation of the π-allyliridium occurs with inversion of stereochemistry, as established in analogous iridium-phosphoramidite-catalyzed processes,[4–12] the stereochemistry of the amination product **4.8a** is consistent with outer-sphere addition of the nitrogen nucleophile. To corroborate this experiment, the amination of allylic acetate **4.1h** was conducted using

the enantiomeric iridium catalyst, (*R*)-Ir-**II** (Scheme 4.3, eq. 5). The amination product **4.8b** is formed with complete alkene (*E*)-stereoselectivity, as determined by ^{1}H NMR. The stereochemistry of **4.8a** is again consistent with outer-sphere C–N bond formation.

Scheme 4.3 Iridium-Catalyzed Amination of Enantiomerically Enriched Deuterated Allylic Acetate **4.1h** with the Enantiomeric Catalysts (*S*)-Ir-**II** (Eq. 4) and (*R*)-Ir-**II** (Eq. 5)[a]

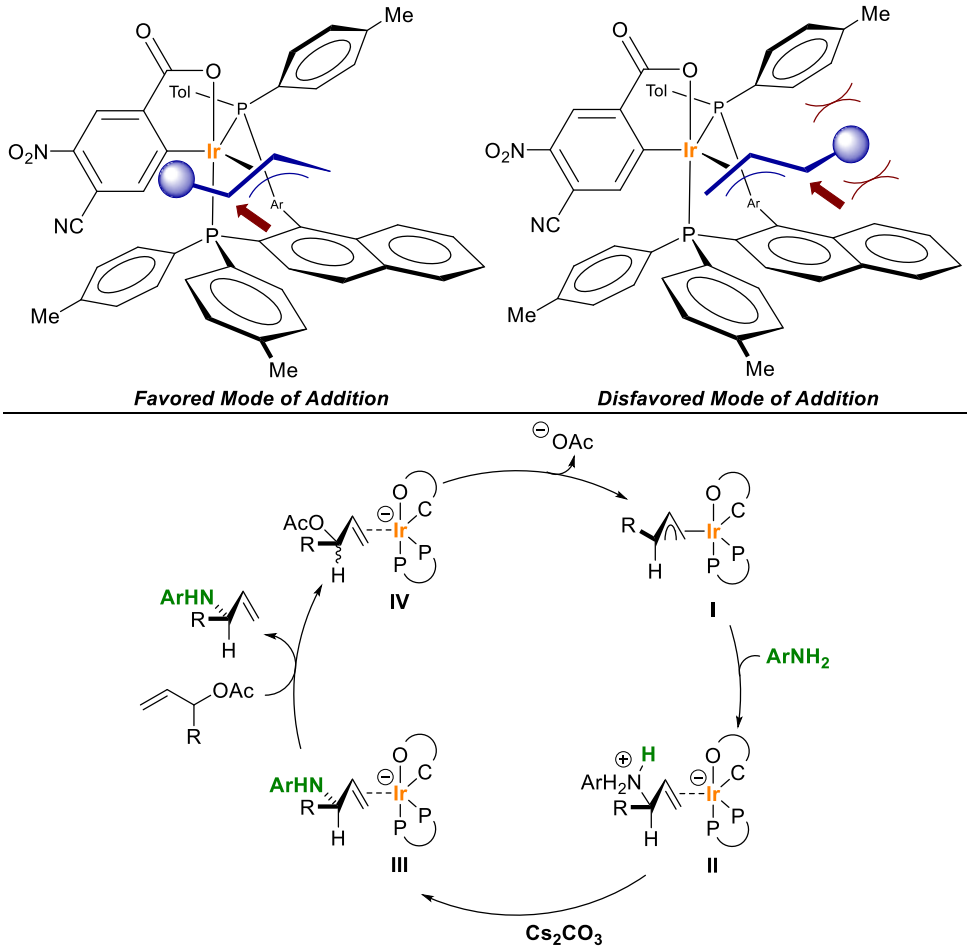


[a]Yield of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

Based on the collective data, a general catalytic mechanism and stereochemical model were proposed (Scheme 4.4). The π-allyliridium(I) complex **I** is subject to outer-sphere amine addition to form the C–N bond and the zwitterionic iridium(I) olefin complex **II**. Deprotonation of ammonium moiety of complex **II** mediated by cesium carbonate generates the anionic iridium(I) species **III**. Alkene exchange with the allylic acetate releases the product of allylic amination and forms the olefin complex **IV**. Loss of acetate ion regenerates the π-allyliridium(I) complex I to close the catalytic cycle. The indicated stereochemical model accounts for the observed sense of absolute stereoinduction for outer

sphere addition of a nucleophile to the neutral iridium π-allyl complex **I**. This model is based upon the coordination mode revealed in closely related crystal structures.[21] Orientation of the π-allyl is controlled through alleviation of steric clashes between the naphthyl and tolyl substituents of the phosphine ligand with the R-group of the resulting π-allyl, as illustrated in the disfavored mode of addition (Scheme 4.4).

Scheme 4.4 General Catalytic Mechanism and Stereochemical Model for Enantioselective Iridium-Catalyzed Allylic Amination



4.4 CONCLUSION

Previously reported enantioselective allylic aminations are largely restricted to chiral iridium–phosphoramidite catalysts.[4–12] In comparison to the initial report from the Krische group on iridium-catalyzed allylic amination, the tol-BINAP-modified complex described above is a significantly more effective catalyst for allylic amination, which has enabled use of primary and secondary aromatic or heteroaromatic amine nucleophiles. These π-allyliridium *C,O*-benzoate catalyzed processes overcome a longstanding limitation associated with all known catalytic systems for asymmetric allylic amination – the ability to promote enantioselective aminations of racemic branched allylic acetates bearing *n*-alkyl groups with complete levels of regioselectivitity.[4–12,16] Another notable feature of these catalysts involves the ability to promote site-selective *N*-allylations of reactants that incorporate both primary and secondary aromatic amines. As demonstrated by mechanistic studies involving amination of the enantiomerically enriched deuterated allylic acetate **4.1h**, an outer-sphere mechanism for C–N bond formation is operative. This work, along with the Krische group's prior studies,[15] significantly expands the scope of catalytic asymmetric allylic amination methodology, broadening access to diverse chiral α-stereogenic amines.

4.5 Experimental Details

4.5.1 General Information

All reactions were carried out under inert gas atmosphere (nitrogen or argon) unless otherwise indicated. Resealable pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14-959-35C) and were flame dried followed by cooling in a desiccator or under a stream of inter gas prior to use. All commercial reagents and anhydrous solvents were used as received from vendors (Fischer Scientific, Sigma Aldrich and Combi Blocks) without further purification. The used Iridium catalyst (*S*)-Ir-**II** and (*R*)-Ir-**II** was prepared according to literature known procedures.[21] Cesium carbonate was used as received from Rockwell Lithium. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still[22] or on a Teledyne Isco Combiflash R_f utilizing Silicycle HP columns using a mobile phase composed of either heptane/isopropyl acetate, heptanes/ethyl acetate or dichloromethane/methanol. Reactions were monitored by a Shimadzu LCMS/UV system with LC-30AD solvent pump, 2020 MS, Sil-30AC autosampler, SPD-M30A UV detector, CTO-20A column oven, using a 2-98% acetonitrile/0.1% formic acid (or 0.001% ammonia) gradient over 2.5 minutes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Absorbents F). Visualization was accomplished with UV light followed by dipping in CAM, *p*-Anisaldehyde (PAA), or $KMnO_4$ stain solution followed by heating.

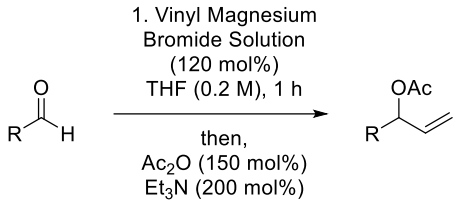
4.5.2 Spectroscopy, Spectrometry, and Data Collection

Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer using a diamond ATR unit. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. Nuclear magnetic resonance (^{1}H, ^{13}C, ^{19}F NMR) spectra were recorded with a Bruker BioSpin GmbG, Varian Gemini (400 MHz) or Varian INOVA (500 MHz) spectrometer equipped with a Bruker cryoprobe. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Specific optical rotations were recorded on an Atago AP-300 automatic polarimeter at the sodium line (589 nm) in CHCl3. Solution concentrations are given in the units of 10^{-2} g mL^{-1}.

4.5.3 Experimental Details and Spectral Data

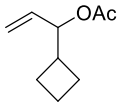
4.5.3.1 Synthesis of Allylic Acetates 4.1[e–g]

The allylic acetates **4.1[e–g]** were prepared by the Grignard reaction and acetylation of the as shown below. The allylic acetates **4.1b**,[23] **4.1c**,[24] and **4.1d**[25] were identical in all respects to the reported materials.



To a round-bottomed flask charged with the corresponding aldehyde under an argon atmosphere was added THF (0.2 M). The reaction flask was placed an ice batch. After 10 minutes, vinyl magnesium bromide solution (120 mol%, 1.0 M in THF) was added slowly and the mixture was stirred at room temperature for 1 hour, at which point acetic anhydride (150 mol%) and triethylamine (200 mol%) were added and the reaction was stirred vigorously overnight. After water was added, the mixture was transferred to a separatory funnel. The organic layer was extracted with diethyl ether and the combined organic layers were washed with 1N HCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography give the corresponding allylic acetate over 2 steps.

1-cyclobutylallyl acetate (4.1e)



4.1e

The title compound was prepared by the general procedure.

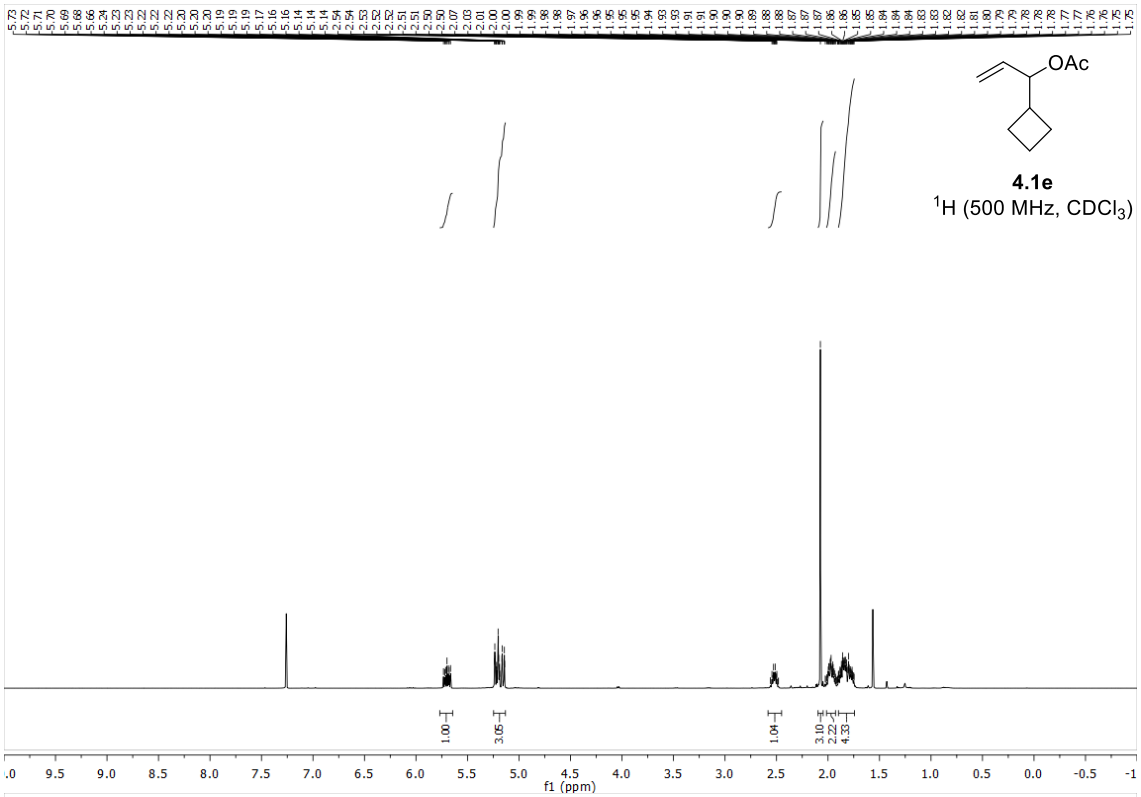
TLC (SiO_2) R_f = 0.61 (heptanes: isopropyl acetate = 4:1).

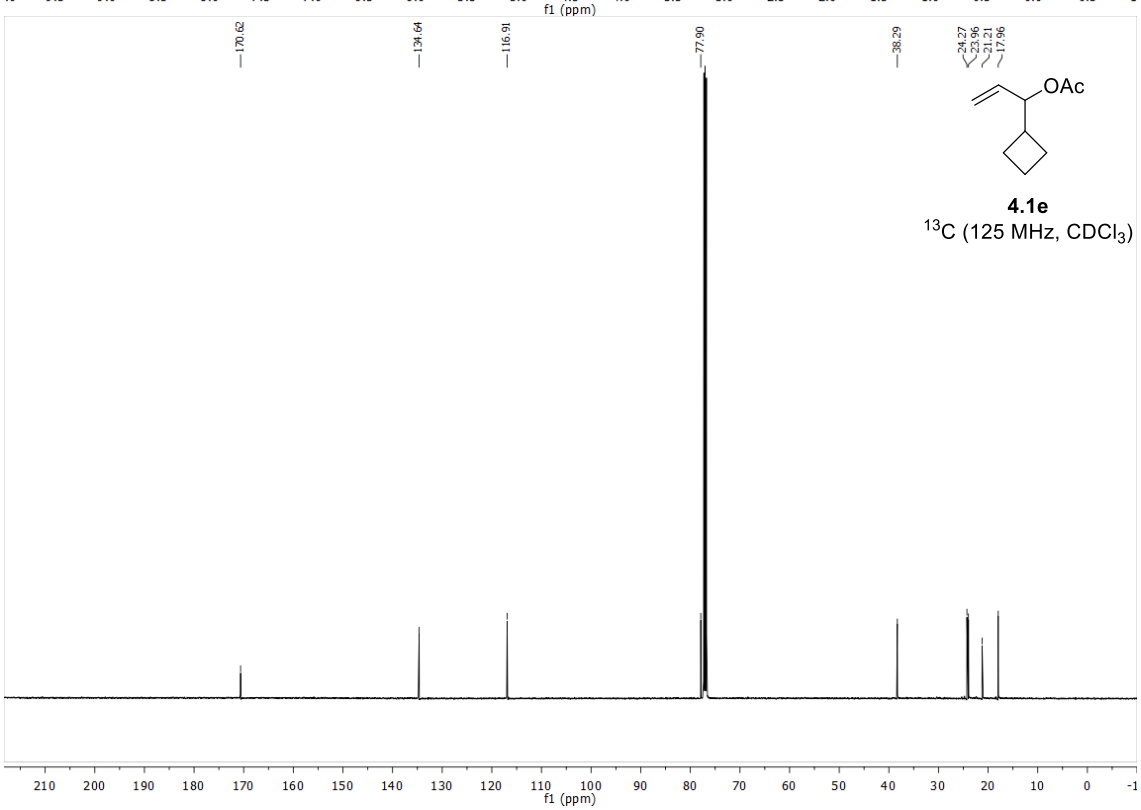
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (ddd, J = 17.2, 10.5, 6.3 Hz, 1H), 5.25 – 5.13 (m, 3H), 2.58 – 2.45 (m, 1H), 2.07 (s, 3H), 1.97 (dddd, J = 18.3, 9.9, 8.0, 4.7 Hz, 2H), 1.90 – 1.74 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 134.6, 116.9, 77.9, 38.3, 24.3, 24.0, 21.2, 18.0.

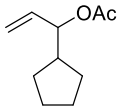
LRMS (CI): Calculated for C_7H_{11} $[M–OAc]^+$ = 95, Found 95.

FTIR (neat): 2941, 1737, 1370, 1232, 1102, 1018, 972, 925 cm^{-1}.


OAc
4.1e
^{1}H (500 MHz, $CDCl_3$)
1.00
3.05
1.04
3.10
2.22
4.33
f1 (ppm)


170.62
134.64
116.91
77.90
38.29
24.27
23.96
21.21
17.96
OAc
4.1e
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

1-cyclopentylallyl acetate (4.1f)



4.1f

The title compound was prepared by the general procedure.

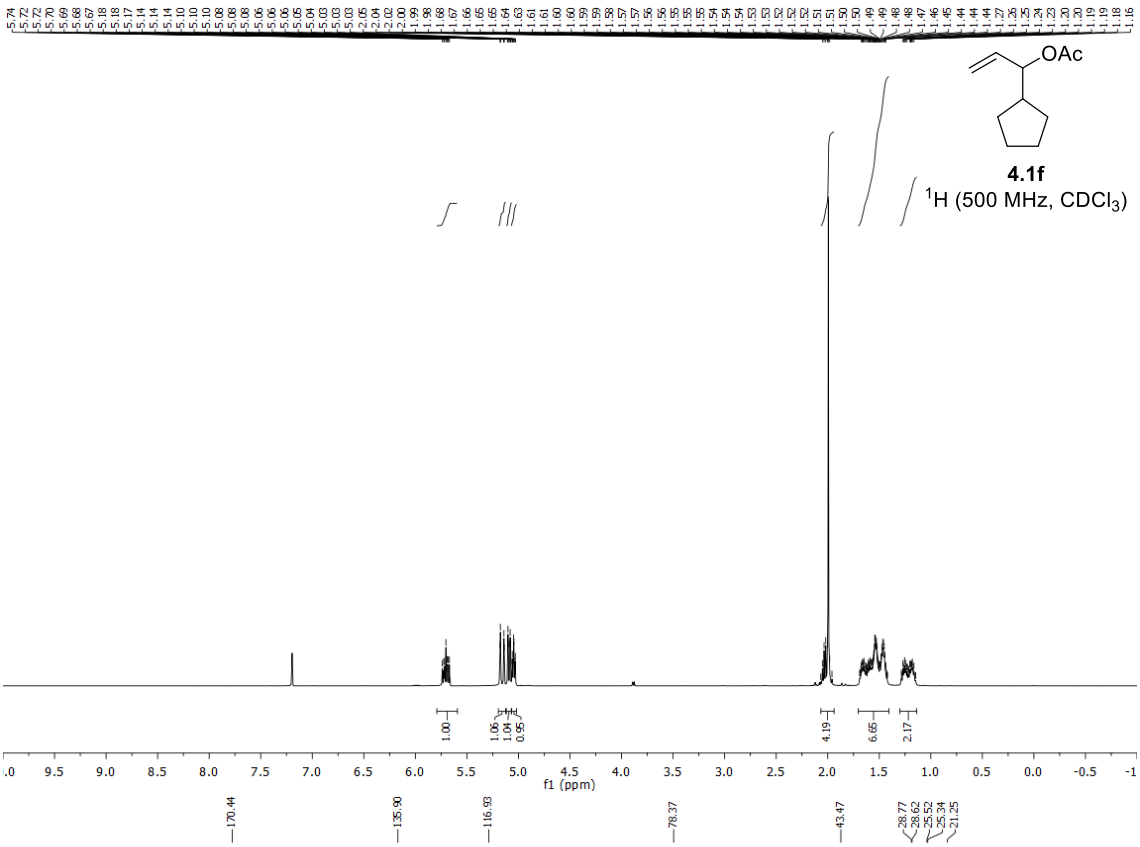
TLC (SiO_2) R_f = 0.61 (heptanes: isopropyl acetate = 4:1).

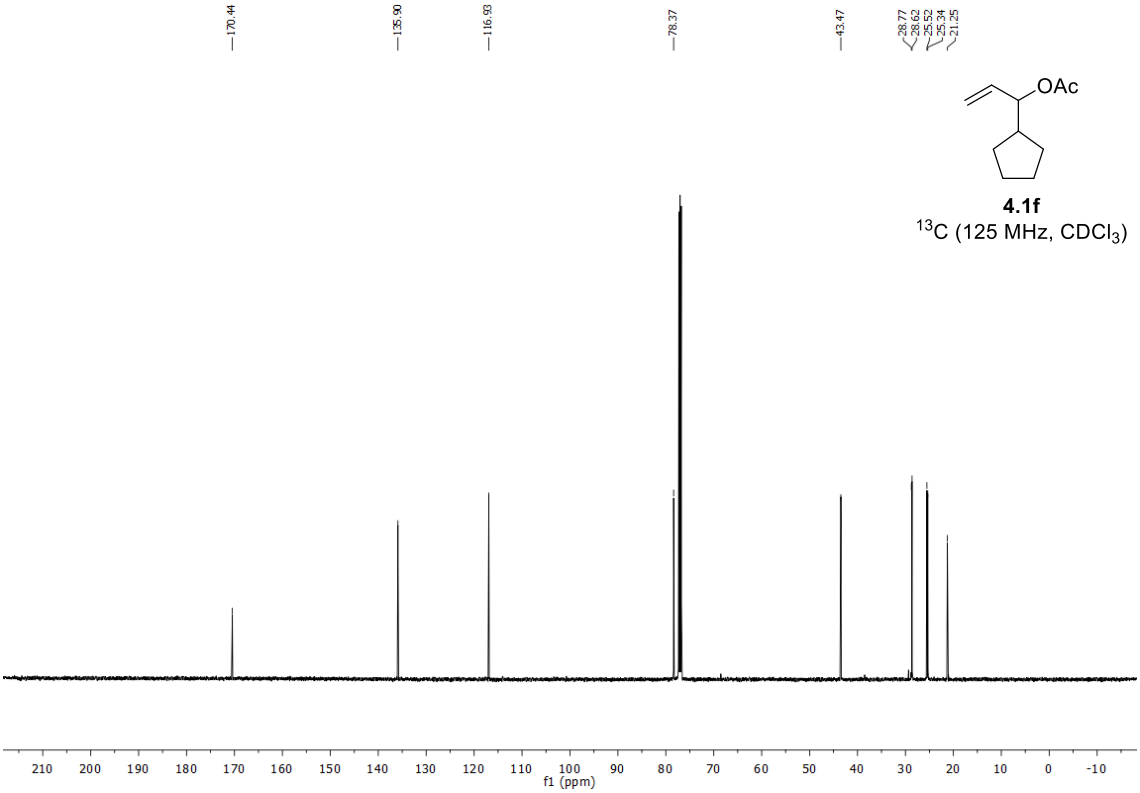
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (ddd, J = 17.2, 10.5, 6.7 Hz, 1H), 5.16 (dt, J = 17.2, 1.4 Hz, 1H), 5.09 (dt, J = 10.6, 1.3 Hz, 1H), 5.07 – 5.02 (m, 1H), 2.07 – 1.94 (m, 4H), 1.70 – 1.41 (m, 6H), 1.30 – 1.14 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 135.9, 116.9, 78.4, 43.5, 28.8, 28.6, 25.5, 25.3, 21.3.

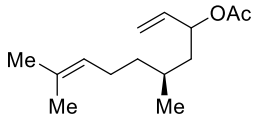
LRMS (CI): Calculated for C_8H_{13} $[M–OAc]^+$ = 109, Found 109.

FTIR (neat): 2954, 2869, 1738, 1370, 1232, 1018, 929, 893 cm^{-1}.


OAc
4.1f
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)


OAc
4.1f
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

(5*S*)-5,9-dimethyldeca-1,8-dien-3-yl acetate (4.1g)



4.1g

The title compound was prepared by the general procedure.

TLC (SiO_2) R_f = 0.46 (heptane: isopropyl acetate = 9:1).

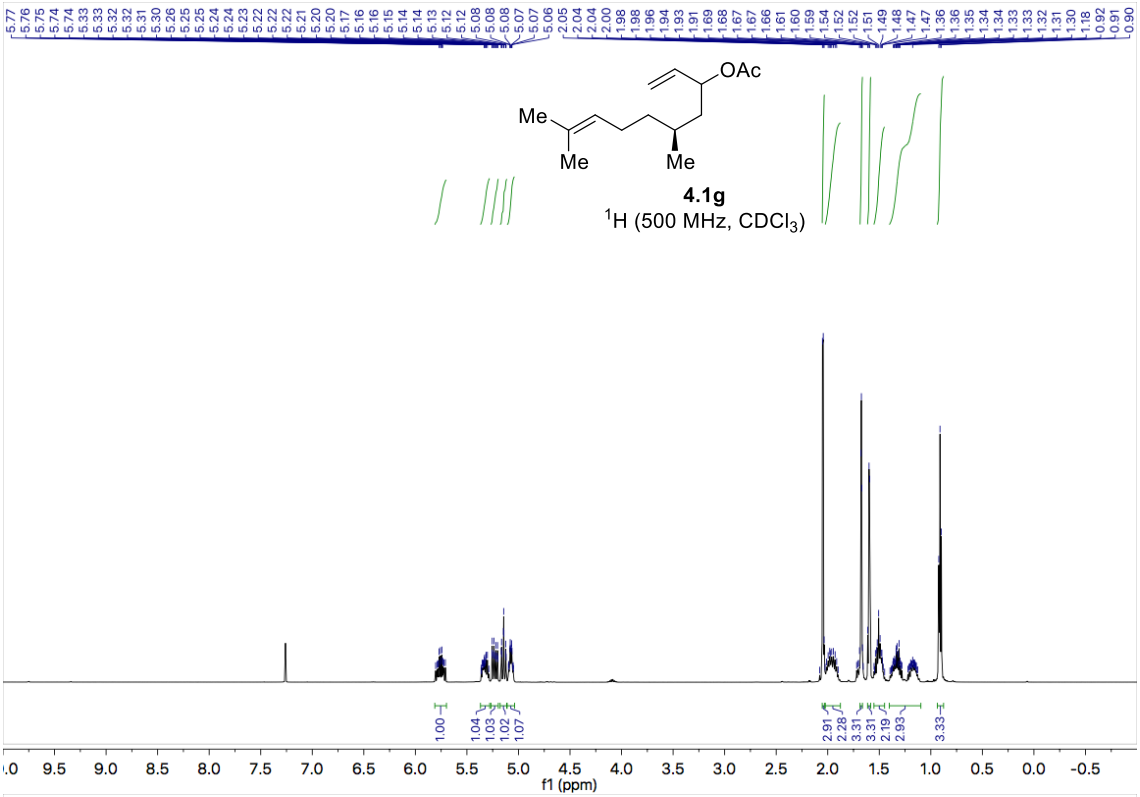
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (dddd, *J* = 17.2, 13.3, 10.5, 6.5 Hz, 1H), 5.38 – 5.27 (m, 1H), 5.23 (ddt, *J* = 17.2, 8.7, 1.3 Hz, 1H), 5.14 (tt, *J* = 10.5, 1.2 Hz, 1H), 5.08 (tdd, *J* = 8.4, 4.9, 3.5 Hz, 1H), 2.05 (d, *J* = 3.9 Hz, 3H), 2.02-1.87 (m, 2H), 1.67 (s, 3H), 1.60 (d, *J* = 3.1 Hz, 3H), 1.55-1.45 (m, 2H), 1.40-1.10(m, 3H), 0.91 (t, *J* = 6.4 Hz, 3H).

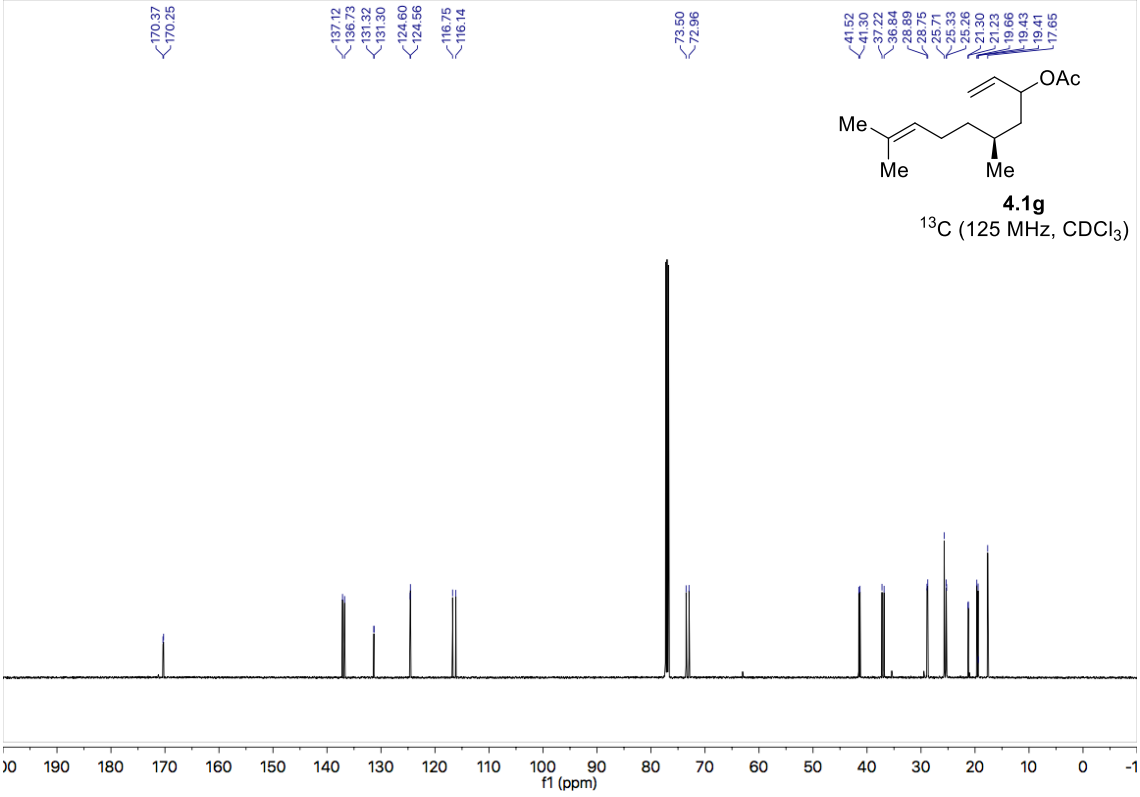
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (d, *J* = 14.9 Hz), 136.9 (d, *J* = 48.9 Hz), 131.3 (d, *J* = 2.2 Hz), 124.6 (d, *J* = 5.1 Hz), 116.4 (d, *J* = 76.0 Hz), 73.2 (d, *J* = 68.0 Hz), 41.4 (d, *J* = 28.2 Hz), 37.0 (d, *J* = 48.7 Hz), 28.8 (d, *J* = 18.5 Hz), 25.7, 25.3 (d, *J* = 8.3 Hz), 21.3 (d, *J* = 8.2 Hz), 19.6 (d, *J* = 29.8 Hz), 17.7.

HRMS (CI): Calculated for $C_{14}H_{24}O_2$ $[M–OAc]^+$ = 165.1643, Found 165.1635.

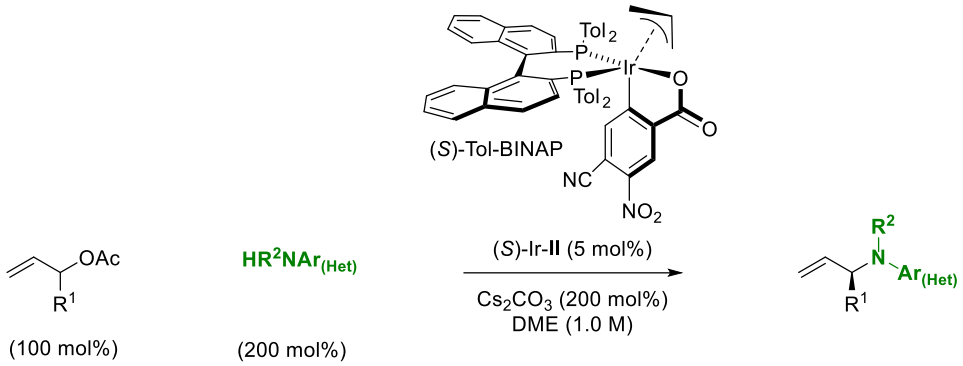
FTIR (neat): 2965, 2917, 2367, 1741, 1338, 1372, 1237, 1020, 988, 929, 668 cm^{-1}.

$[\alpha]_D^{28}$= –3.56 (*c* 0.2, $CHCl_3$).


OAc
Me
Me
Me
4.1g
^{1}H (500 MHz, $CDCl_3$)
f1 (ppm)

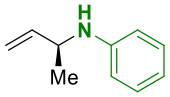

OAc
Me
Me
Me
4.1g
^{13}C (125 MHz, $CDCl_3$)
f1 (ppm)

4.5.3.2 General Procedure and Spectral Data for Synthesis of Allylic Amines 4.4[a–l], 4.5[a–l], 4.6[a–g], and 4.7[a–c]



A pressure tube equipped with a magnetic stir bar was charged with cesium carbonate (200 mol%), (*S*)-Ir-**II** (5 mol%). The tube was purged with argon for 5 minutes. DME (1.0 M) was added followed by the allylic acetate (100 mol%) and the amine (200 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at the indicated temperature and stirred for the indicated period of time. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography.

(*S*)-N-(but-3-en-2-yl)aniline (4.4a)



4.4a

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (81.6 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 82% yield (53.1 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 20 min).

TLC (SiO_2) R_f = 0.40 (heptanes: isopropyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 – 7.09 (m, 2H), 6.68 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.63 – 6.57 (m, 2H), 5.83 (ddd, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.08 (dt, *J* = 10.4, 1.4 Hz, 1H), 3.98 (dddd, *J* = 9.5, 6.6, 4.8, 3.3 Hz, 1H), 3.59 (s, 1H), 1.31 (d, *J* = 6.6 Hz, 3H).

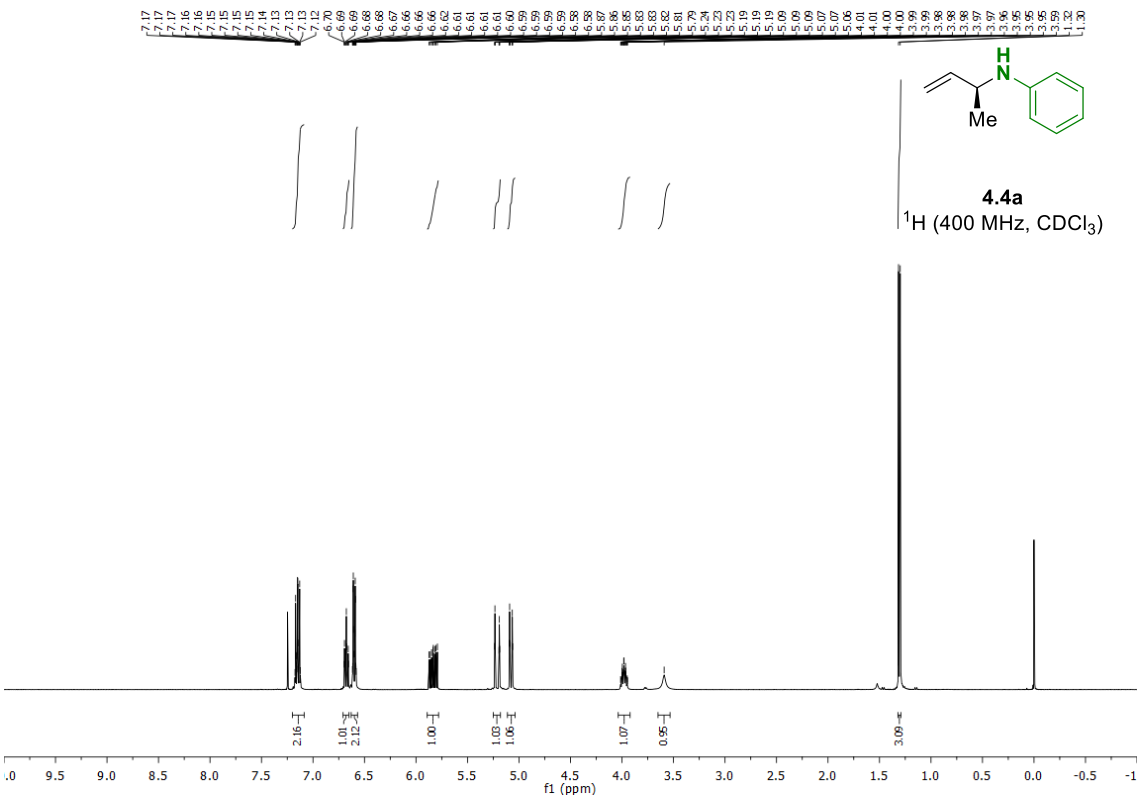
^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 141.3, 129.1, 117.3, 114.1, 113.4, 51.1, 21.6.

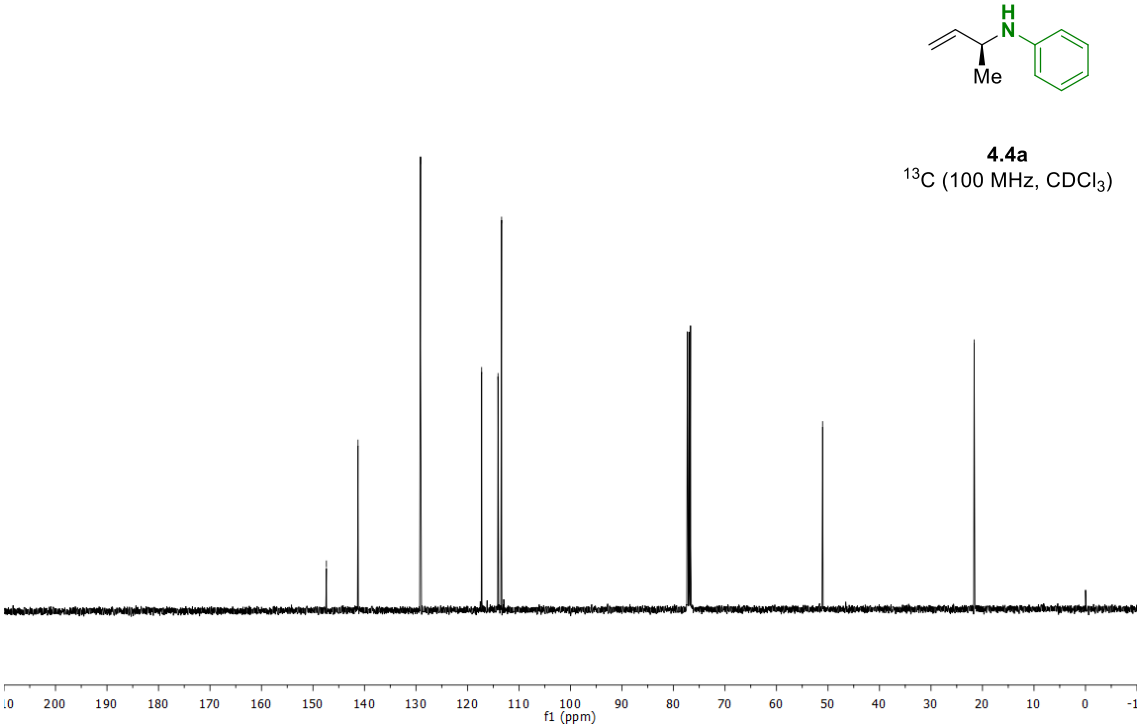
HRMS (ESI): Calculated for $C_{10}H_{13}N$ [M+H$^+$] = 148.1126, Found 148.1122.

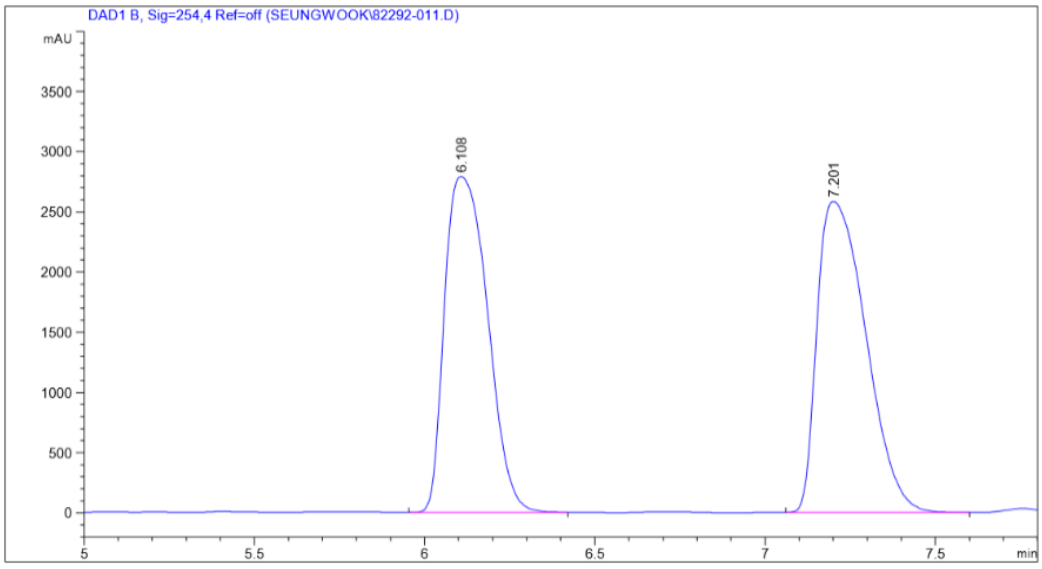
FTIR (neat): 3404, 2975, 1601, 1504, 1317, 1254, 992, 919, 748, 692 cm^{-1}.

$[\alpha]_D^{28}$ = –3.9 (*c* 0.2, $CHCl_3$).

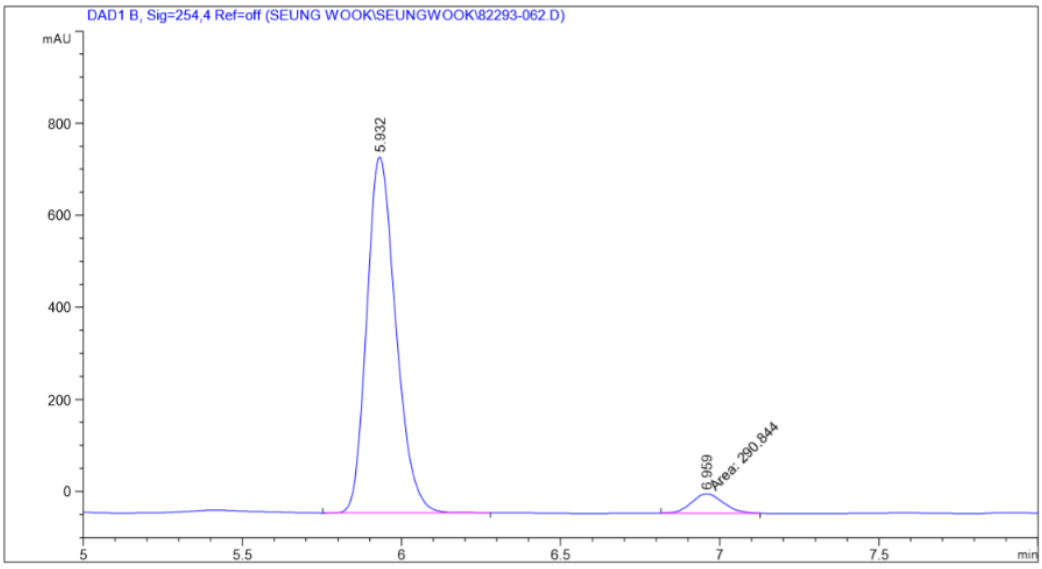
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 97.5:2.5, 1.00 mL/min, 254 nm), *ee* = 89%.


H
N
Me
4.4a
1H (400 MHz, CDCl3)
f1 (ppm)


H
N
Me
4.4a
13C (100 MHz, CDCl3)
f1 (ppm)

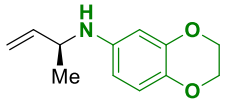


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.108	BB	0.1443	2.44570e4	2790.51685	48.7471
2	7.201	BB	0.1601	2.57142e4	2583.42285	51.2529



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.932	BB	0.0982	4926.29297	774.15454	94.4252
2	6.959	MM	0.1153	290.84390	42.03476	5.5748

(*S*)-N-(but-3-en-2-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine (4.4b)



4.4b

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (133.0 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 24 hr). The title compound was obtained in 85% yield (76.5 mg, 0.37 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 20 min).

TLC (SiO_2) R_f = 0.23 (heptanes: isopropyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (dd, *J* = 8.5, 0.4 Hz, 1H), 6.17 (d, *J* = 2.7 Hz, 1H), 6.14 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.20 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.07 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.34 – 4.18 (m, 2H), 4.21 – 4.13 (m, 2H), 4.00 – 3.77 (m, 1H), 3.33 (br, 1H), 1.28 (d, *J* = 6.6 Hz, 3H).

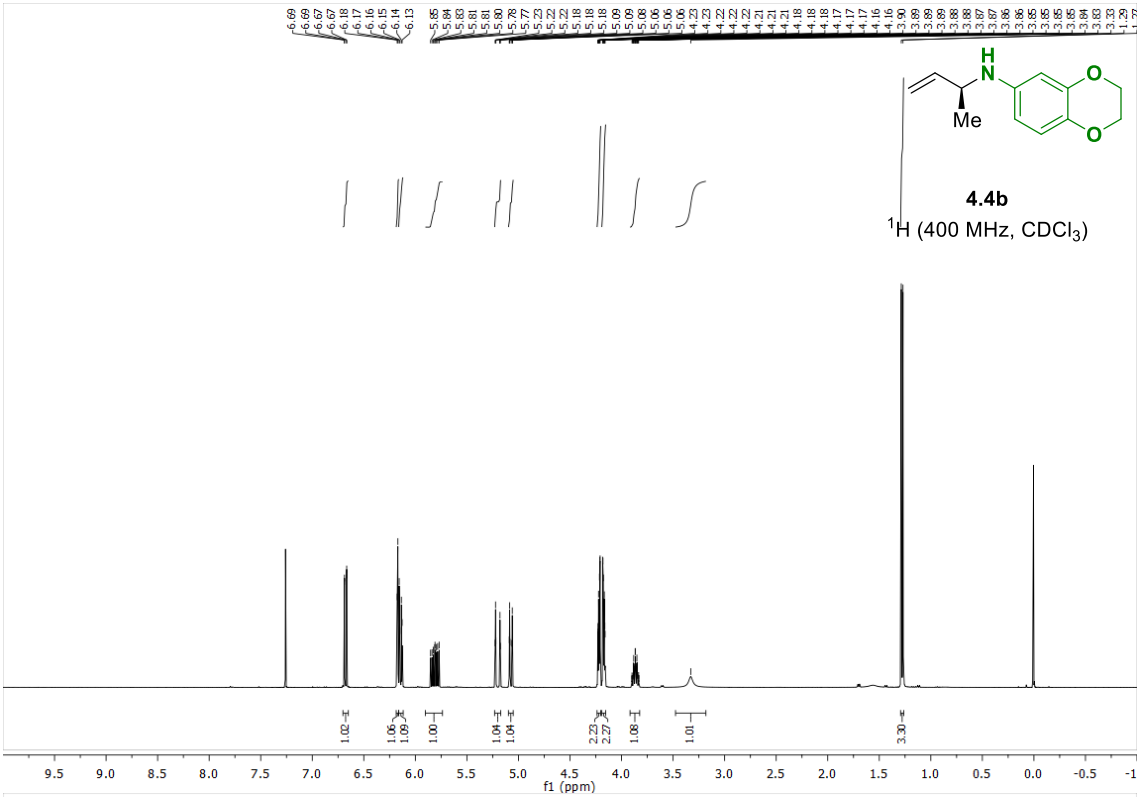
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 142.4, 141.5, 135.5, 117.5, 114.1, 107.4, 102.3, 64.8, 64.2, 51.9, 21.7.

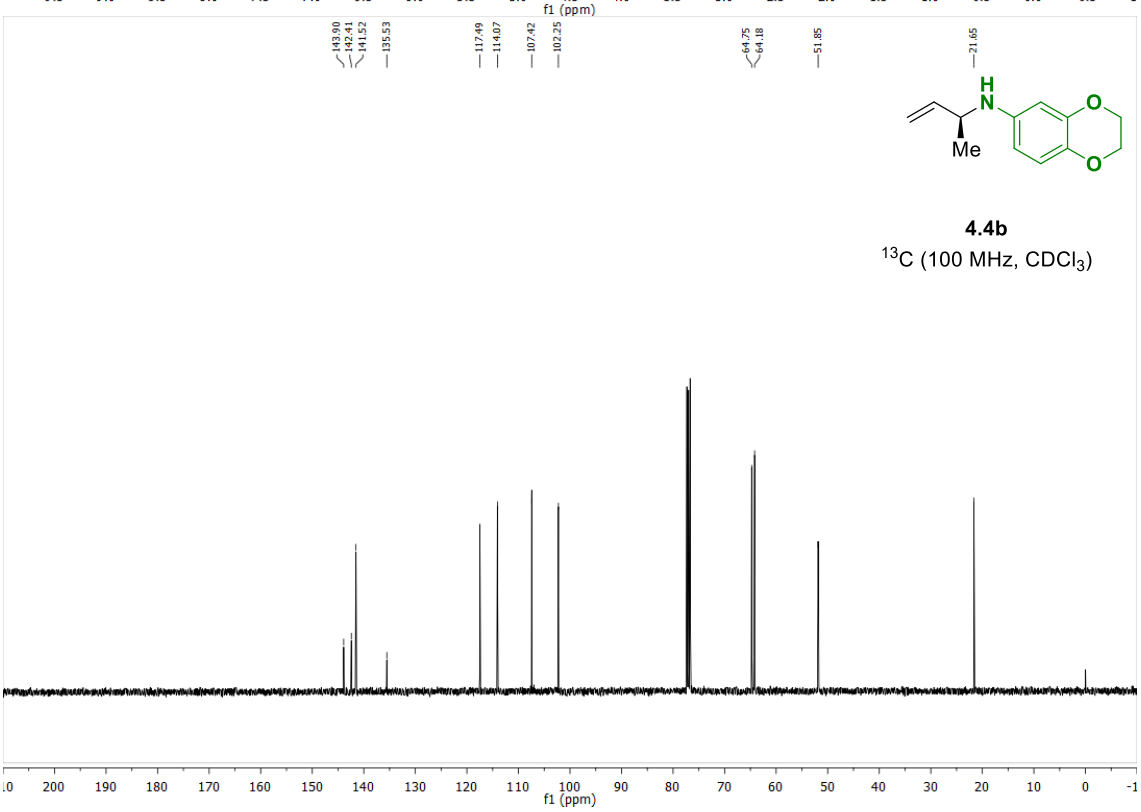
HRMS (ESI): Calculated for $C_{12}H_{15}NO_2$ [M+H$^+$] = 206.1176, Found 206.1183.

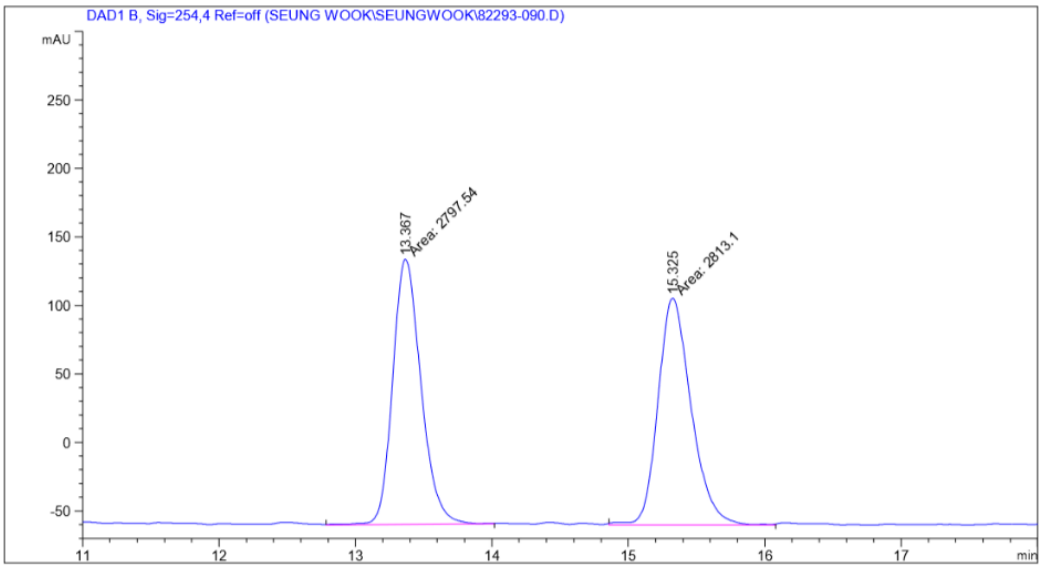
FTIR (neat): 3394, 2973, 1507, 1207, 1068, 915, 884, 794, 740 cm^{-1}.

$[\alpha]_D^{28}$= –0.87 (*c* 0.2, $CHCl_3$).

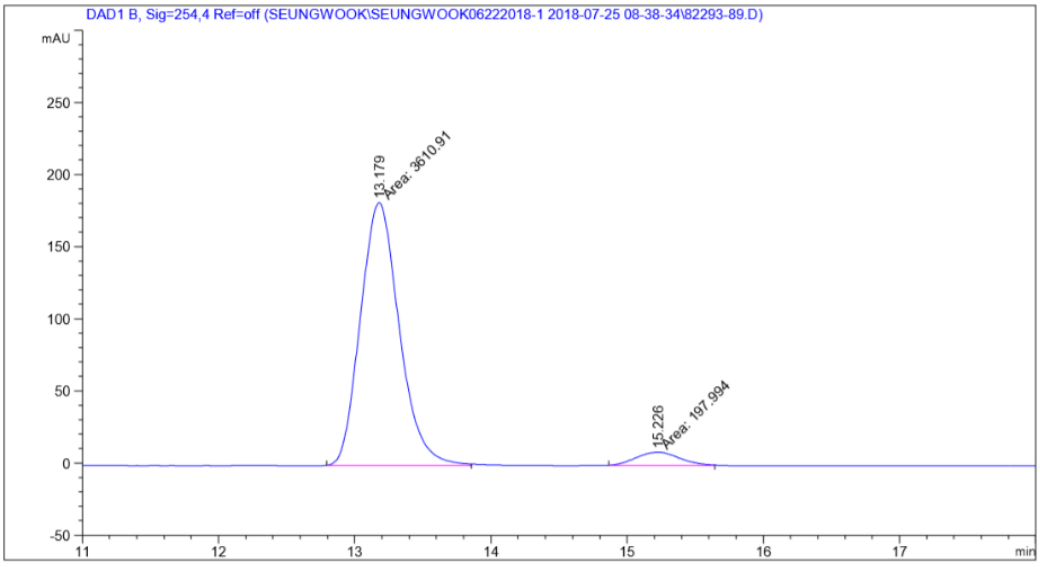
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 97.5:2.5, 1.00 mL/min, 254 nm), *ee* = 90%.


H
N
Me
O
O
4.4b
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


H
N
Me
O
O
4.4b
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

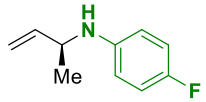


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.367	MM	0.2409	2797.53516	193.58287	49.8613
2	15.325	MM	0.2831	2813.09619	165.62939	50.1387



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.179	MM	0.3303	3610.91309	182.21223	94.8018
2	15.226	MM	0.3657	197.99403	9.02356	5.1982

(*S*)-N-(but-3-en-2-yl)-4-fluoroaniline (4.4c)



4.4c

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (97.8 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 24 hr). The title compound was obtained in 83% yield (60.3 mg, 0.37 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 20 min).

TLC (SiO_2) R_f = 0.36 (heptanes: isopropyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1H NMR (400 MHz, Chloroform-d) δ 6.91 – 6.81 (m, 2H), 6.58 – 6.49 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.01 – 3.83 (m, 1H), 3.48 (br, 1H), 1.31 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 154.5, 143.7, 141.2, 115.6, 115.4, 114.3, 114.2, 51.8, 21.7.

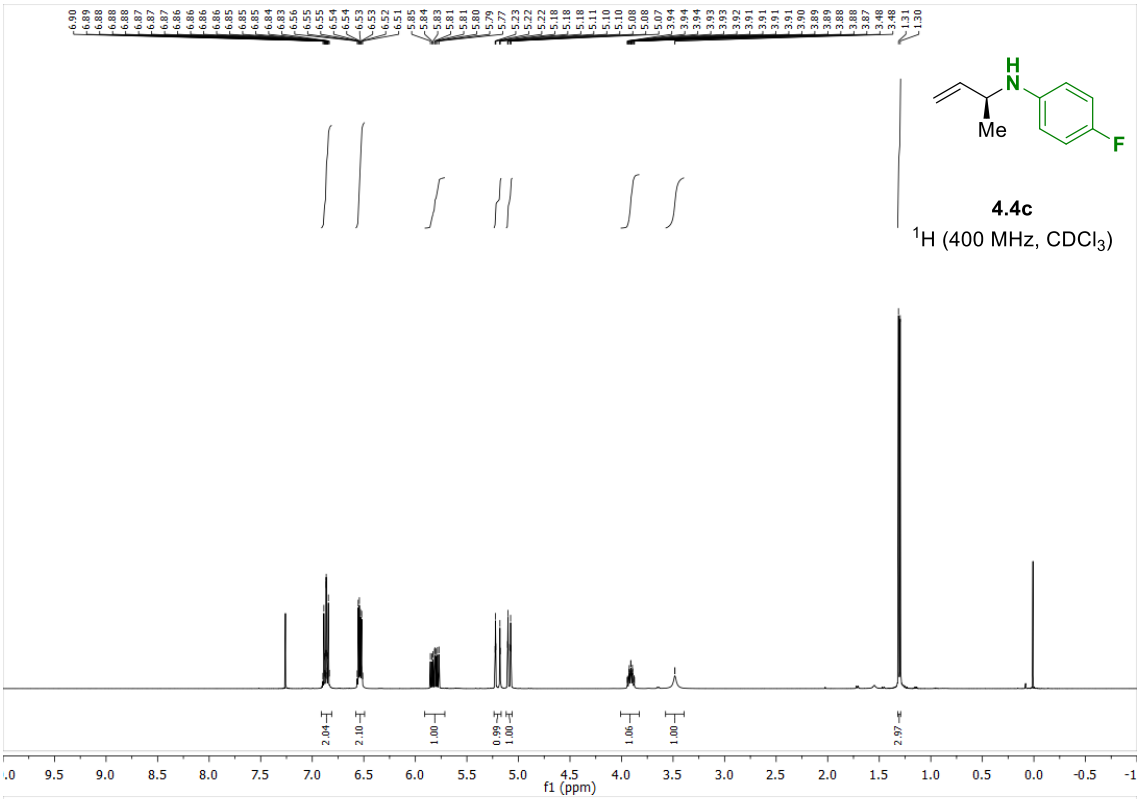
^{19}F NMR (376 MHz, $CDCl_3$): δ = –128.3.

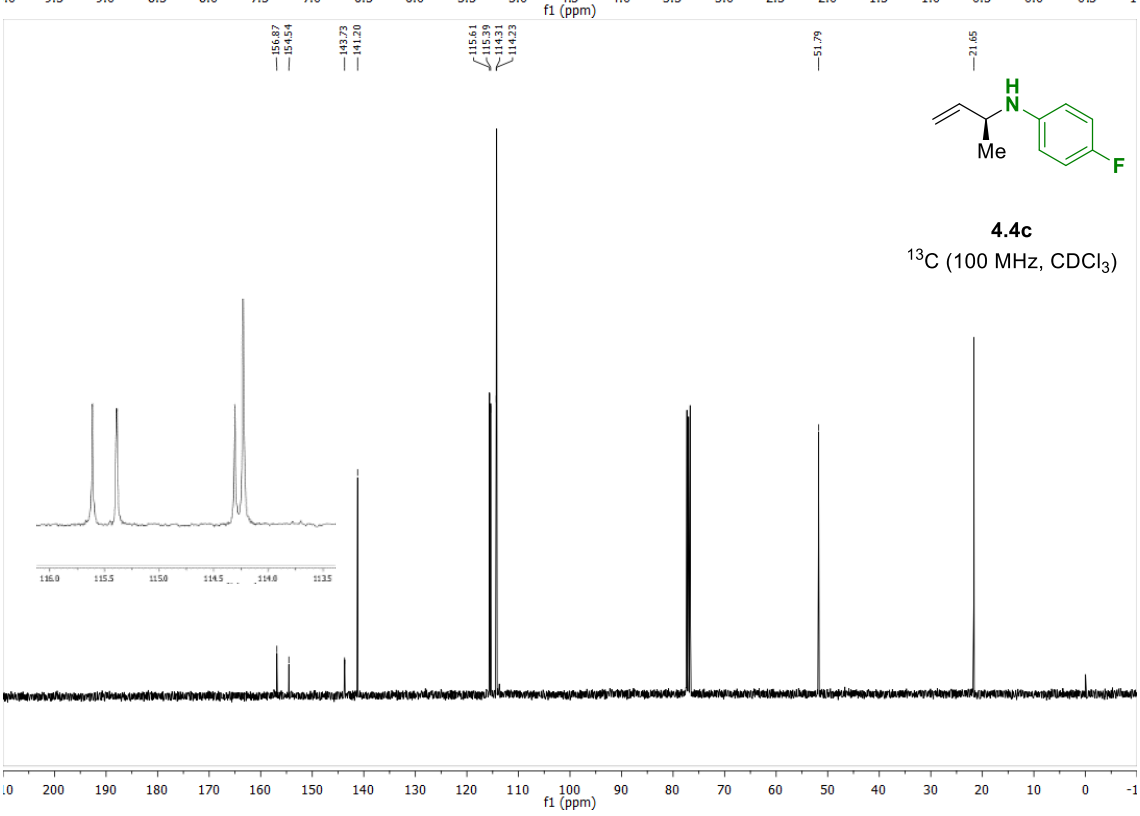
HRMS (ESI): Calculated for $C_{10}H_{12}NF$ [M+H$^+$] = 166.1027, Found 166.1028.

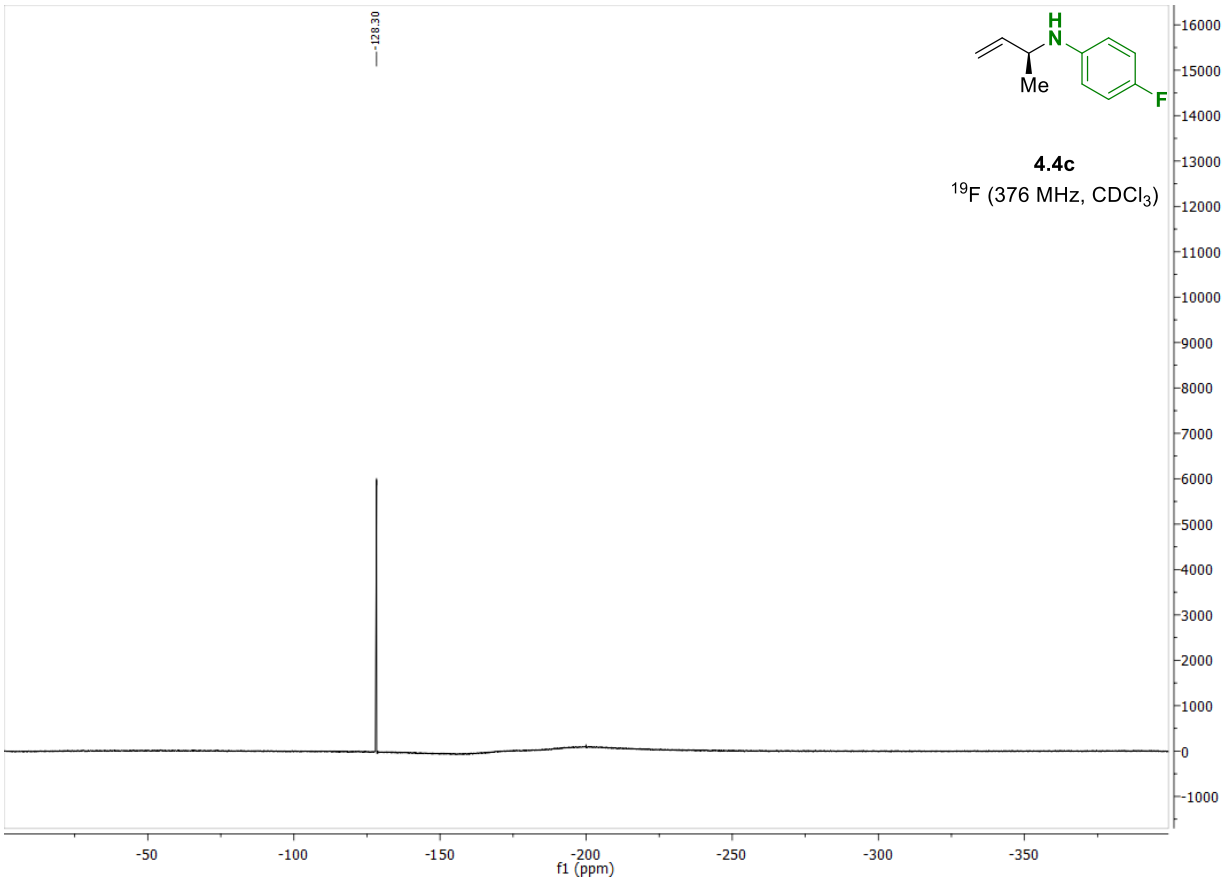
FTIR (neat): 2975, 1505, 1309, 1213, 1155, 991, 918, 815, 770, 506 cm^{-1}.

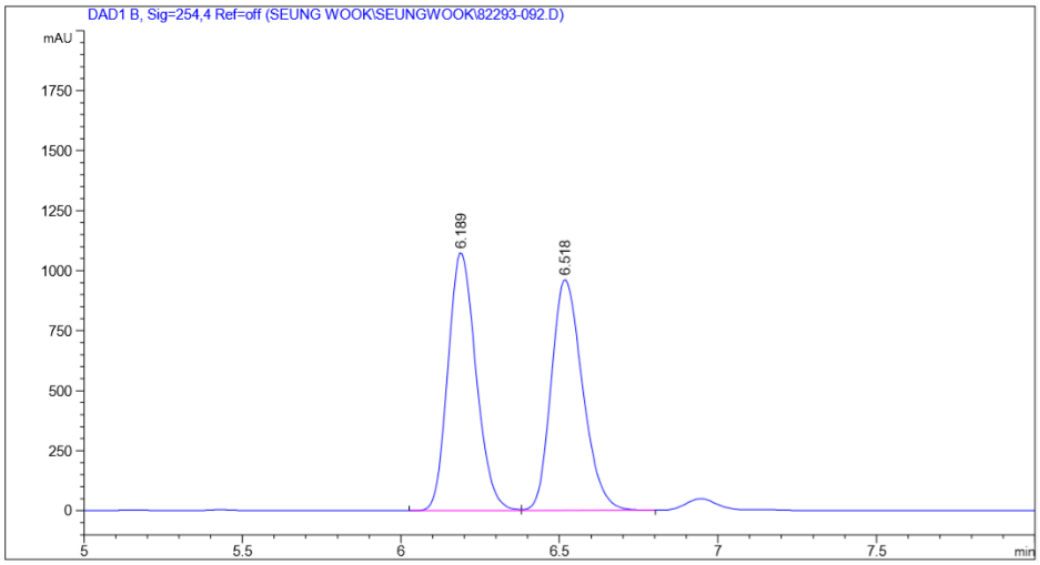
$[\alpha]_D^{28}$ = +1.78 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 90%.

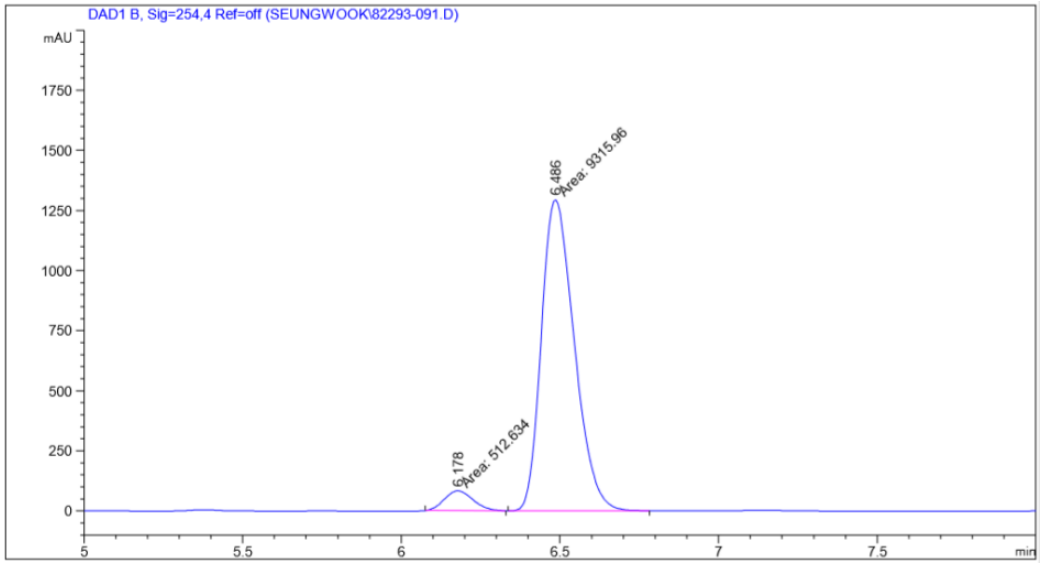

Me
F
4.4c
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


Me
F
4.4c
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)


-128.30
H
N
Me
F
4.4c
19F (376 MHz, CDCl3)
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-50
-100
-150
-200
-250
-300
-350
f1 (ppm)

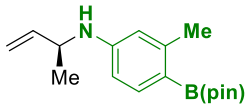


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.189	BV	0.0958	6617.14795	1075.90527	50.0313
2	6.518	VB	0.1061	6608.87158	962.52228	49.9687



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.178	MM	0.1040	512.63373	82.19147	5.2157
2	6.486	MM	0.1198	9315.95605	1295.97278	94.7843

(*S*)-N-(but-3-en-2-yl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (4.4d)



4.4d

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (205.1 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 40 hr). The title compound was obtained in 85% yield (98.6 mg, 0.34 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.58 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.7 Hz, 1H), 6.40 (d, *J* = 7.0 Hz, 2H), 5.83 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.08 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.04 (p, *J* = 6.5 Hz, 1H), 3.74 (br, 1H), 2.47 (s, 3H), 1.33 – 1.29 (m, 15H).

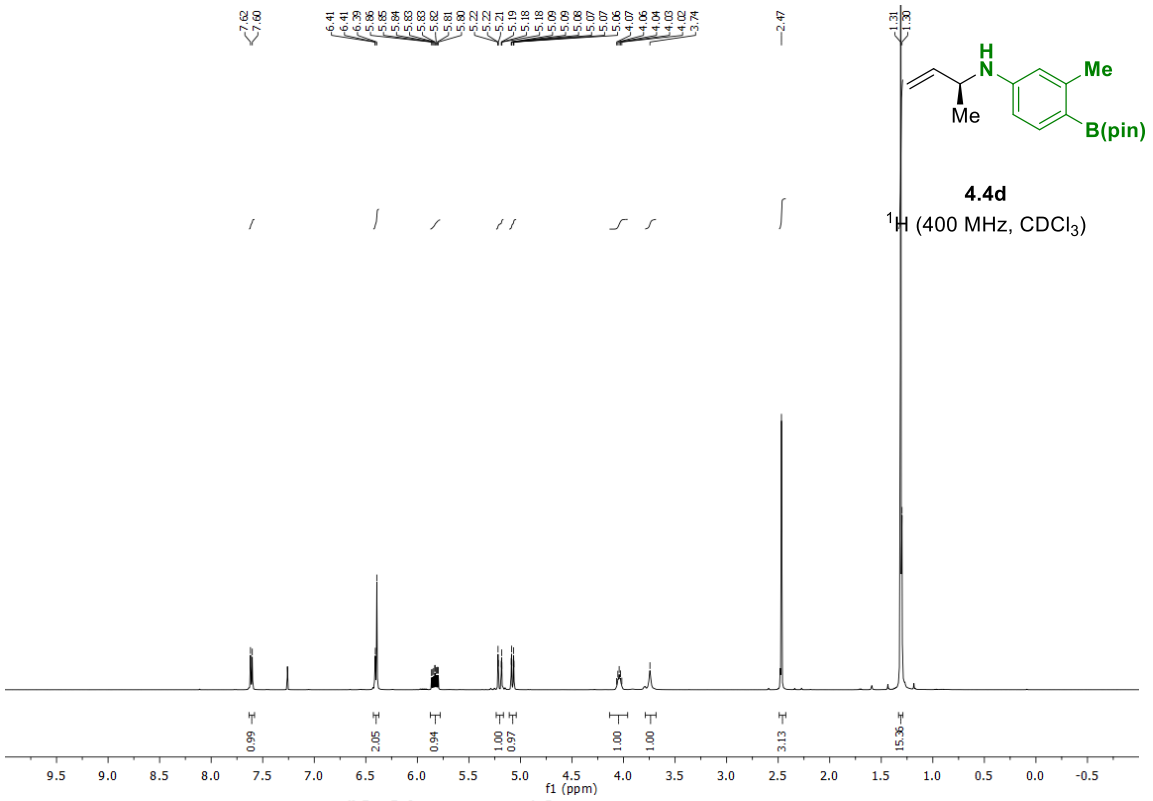
^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 146.7, 140.8, 137.8, 114.5, 114.1, 109.6, 82.7, 50.4, 24.9, 24.9, 22.5, 21.5.

HRMS (ESI): Calculated for $C_{17}H_{26}NO_2$ [M+H$^+$] = 288.2132, Found 288.2138.

FTIR (neat): 2978, 2362, 1602, 1349, 1215, 1146, 754 cm^{-1}.

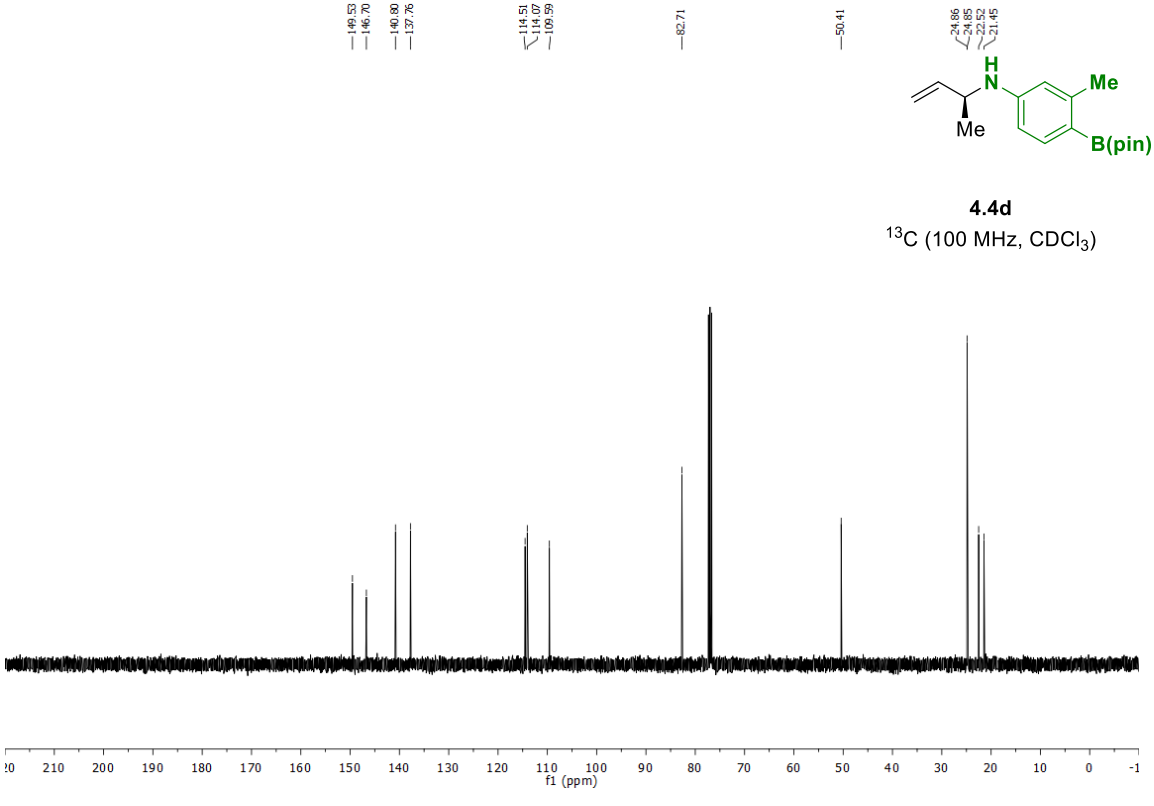
$[\alpha]_D^{28}$= –1.0 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel OD-3 column, hexanes:*i*-PrOH = 97:3, 1.00 mL/min, 280 nm), *ee* = 89%.



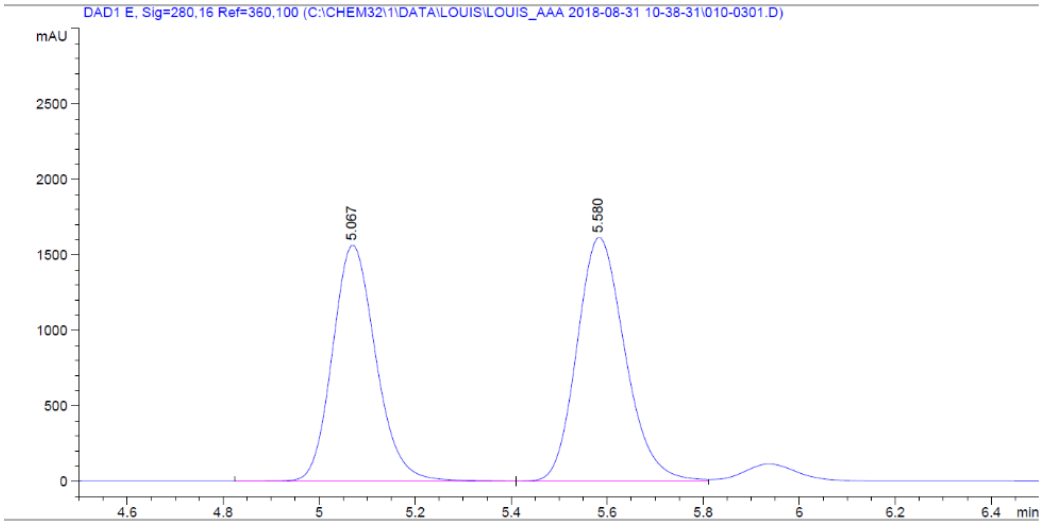
4.4d

^{1}H (400 MHz, $CDCl_3$)

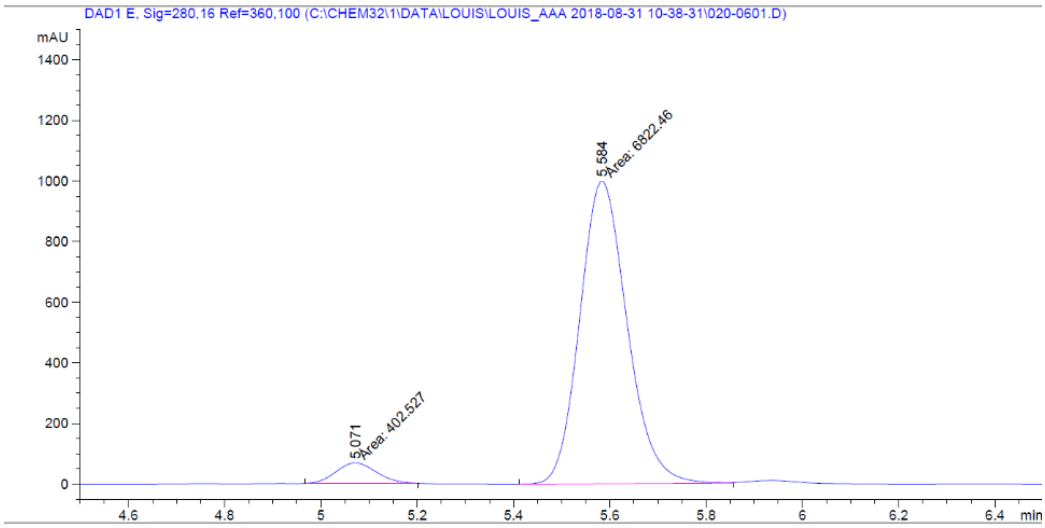


4.4d

^{13}C (100 MHz, $CDCl_3$)

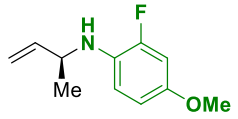


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.067	VV	0.0972	9832.24707	1566.88391	46.6365
2	5.580	VV	0.1091	1.12505e4	1618.21069	53.3635



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.071	MM	0.0981	402.52716	68.38924	5.5713
2	5.584	MM	0.1136	6822.46045	1000.98846	94.4287

(*S*)-N-(but-3-en-2-yl)-2-fluoro-4-methoxyaniline (4.4e)



4.4e

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (124.2 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 78% yield (67.1 mg, 0.34 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.58 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 – 6.60 (m, 2H), 6.56 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.82 (ddd, *J* = 16.7, 10.3, 5.8 Hz, 1H), 5.20 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.08 (dd, *J* = 10.4, 1.4 Hz, 1H), 3.91 (p, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 3.52 (br, 1H), 1.33 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.08, 151.5 (d, *J* = 9.9 Hz), 150.71, 141.28, 129.7 (d, *J* = 12.1 Hz), 114.4 (d, *J* = 4.6 Hz), 114.19, 109.1 (d, *J* = 3.3 Hz), 102.38 (d, *J* = 22.7 Hz), 55.8, 51.9, 21.7.

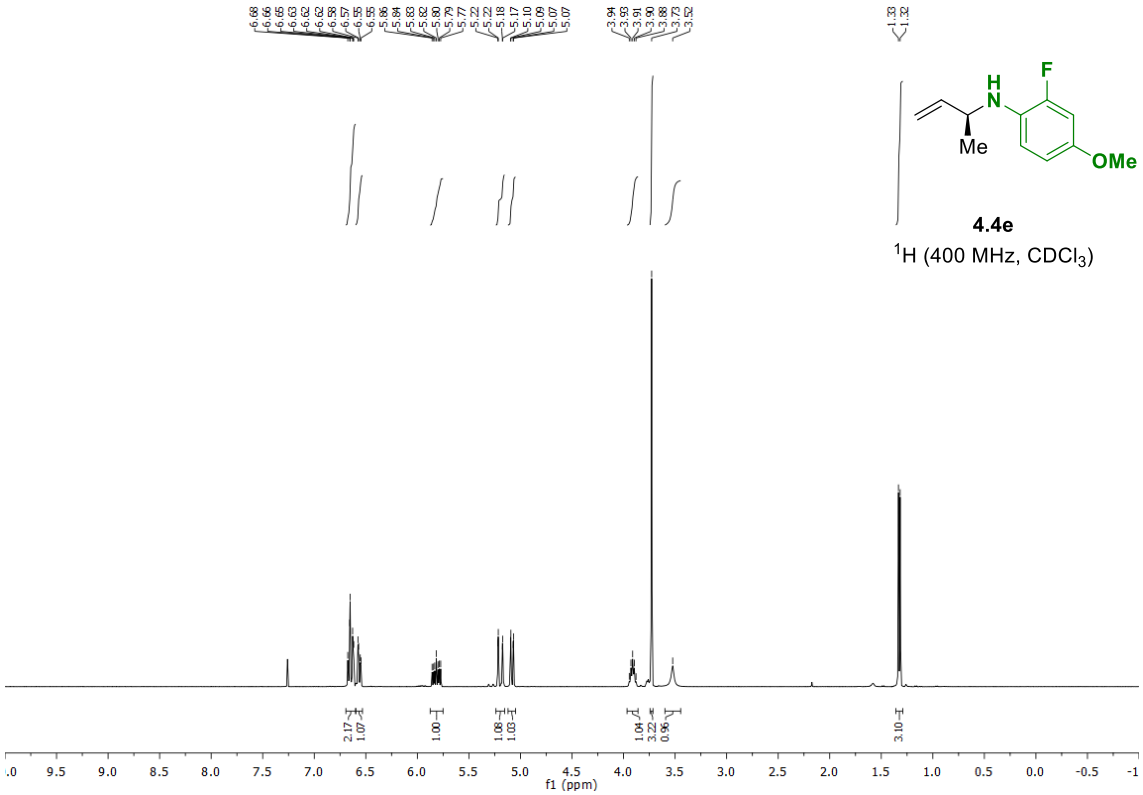
^{19}F NMR (471 MHz, $CDCl_3$): δ = –133.0 (dd, *J* = 12.9, 9.8 Hz, 1F).

HRMS (ESI): Calculated for $C_{11}H_{14}FNO$ [M+H$^+$] = 196.1132, Found 196.1129.

FTIR (neat): 2964, 1515, 1279, 1214, 1152, 1035, 923, 755 cm^{-1}.

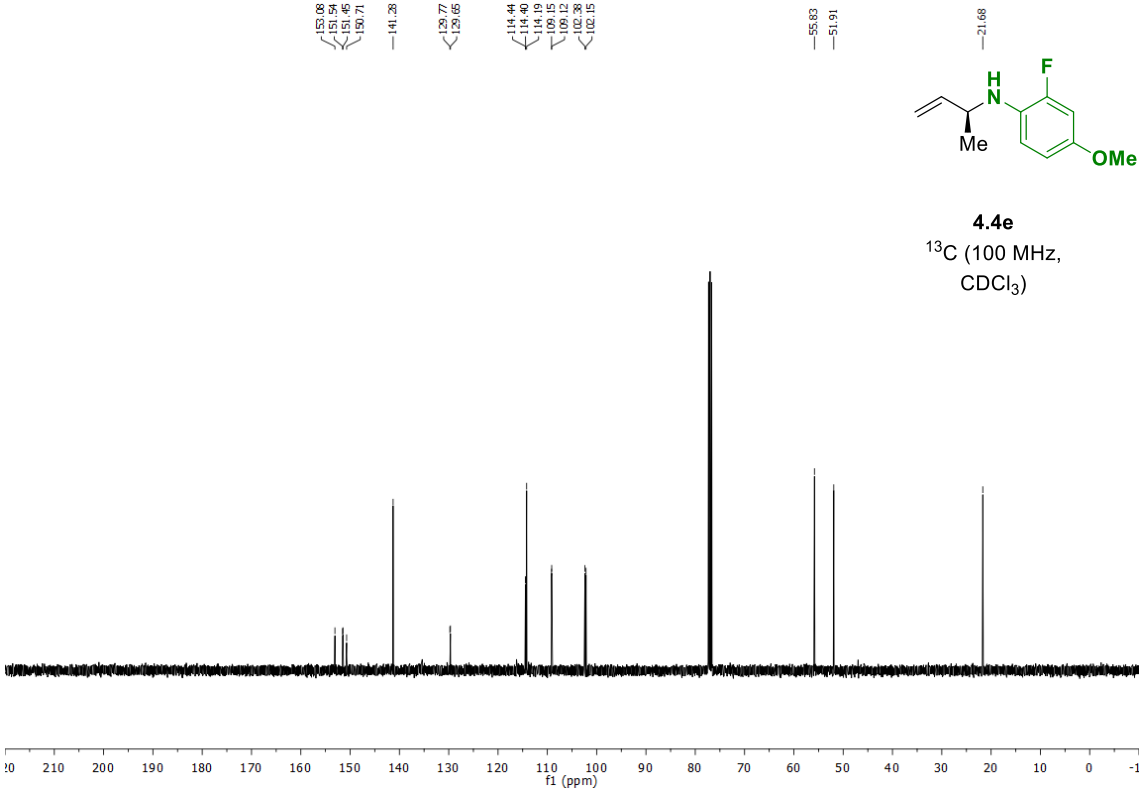
$[\alpha]_D^{28}$ = +6.3 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 88%.



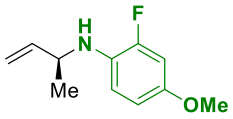
4.4e

^{1}H (400 MHz, $CDCl_3$)



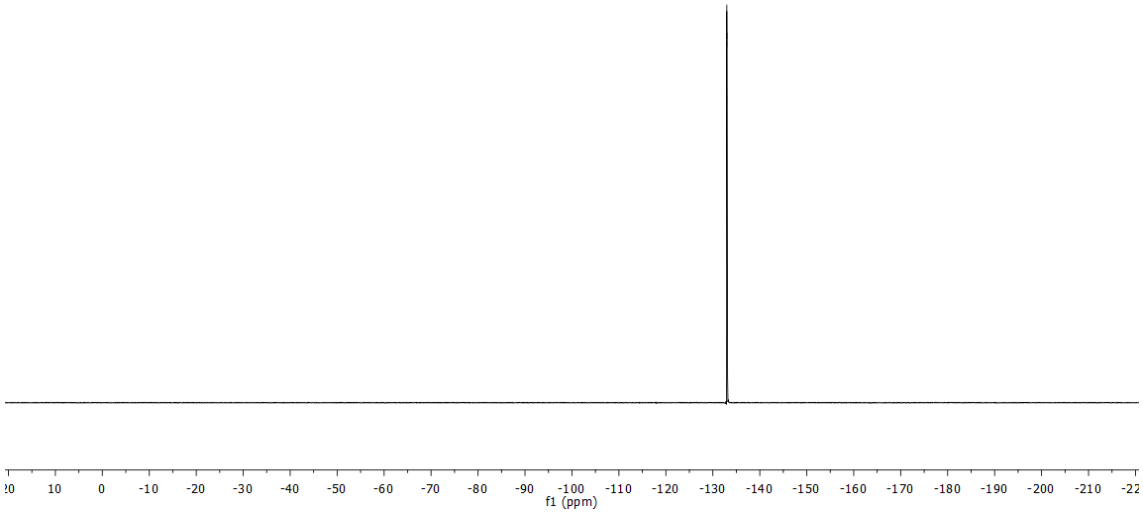
4.4e

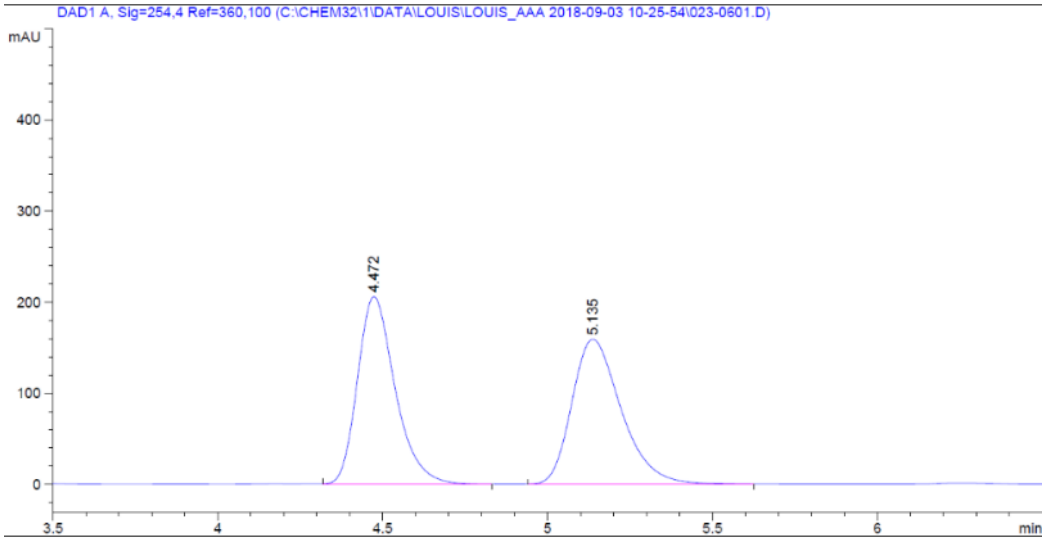
^{13}C (100 MHz, $CDCl_3$)



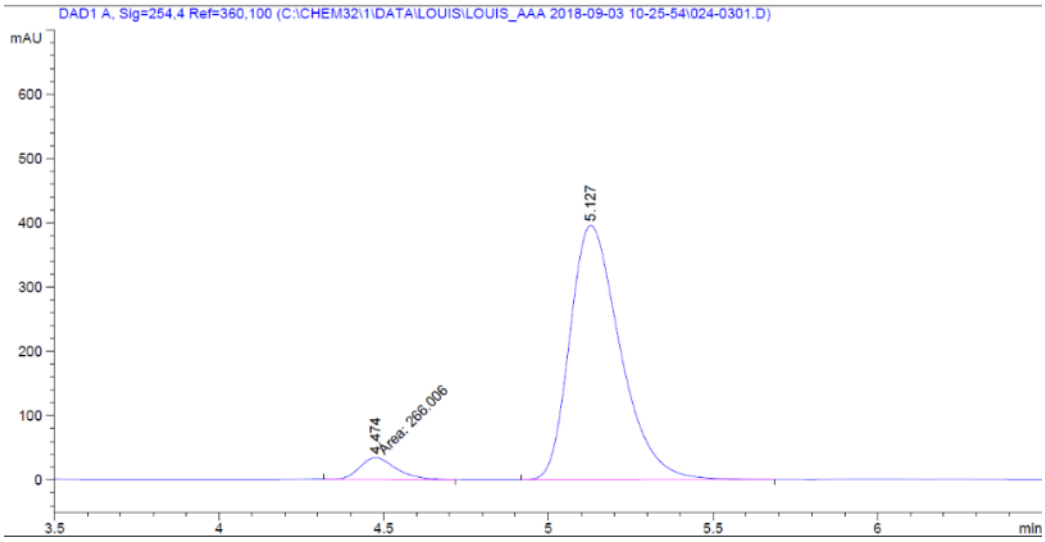
4.4e

^{19}F (376 MHz, $CDCl_3$)



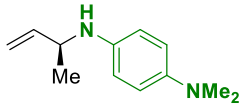


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.472	BB	0.1229	1642.40771	206.31035	49.6953
2	5.135	BB	0.1598	1662.54736	159.29028	50.3047



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.474	MM	0.1299	266.00577	34.12355	5.9477
2	5.127	BB	0.1639	4206.39307	396.07928	94.0523

(*S*)-N1-(but-3-en-2-yl)-N4,N4-dimethylbenzene-1,4-diamine (4.4f)



4.4f

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (120.0 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 89% yield (74.5 mg, 0.39 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 10:1–4:1).

TLC (SiO_2) R_f = 0.34 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 – 6.68 (m, 2H), 6.64 – 6.57 (m, 2H), 5.84 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.06 (dt, *J* = 10.4, 1.4 Hz, 1H), 3.90 (ttd, *J* = 6.6, 5.3, 1.3 Hz, 1H), 3.25 (br, 1H), 2.81 (s, 6H), 1.28 (d, *J* = 6.6 Hz, 3H).

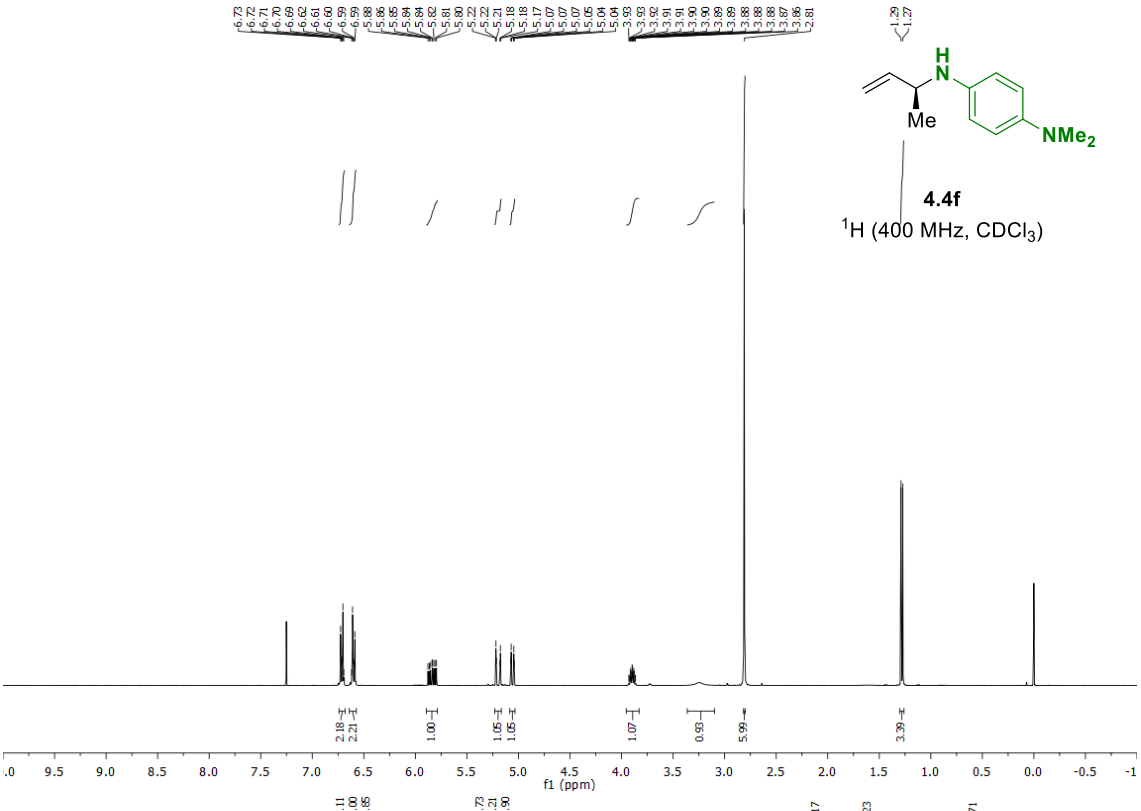
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 142.0, 139.9, 115.7, 115.2, 113.9, 52.2, 42.2, 21.7.

HRMS (ESI): Calculated for $C_{12}H_{18}N_2$ [M+H$^+$] = 191.1543, Found 191.1535.

FTIR (neat): 2979, 2361, 1515, 1216, 814, 753 cm^{-1}.

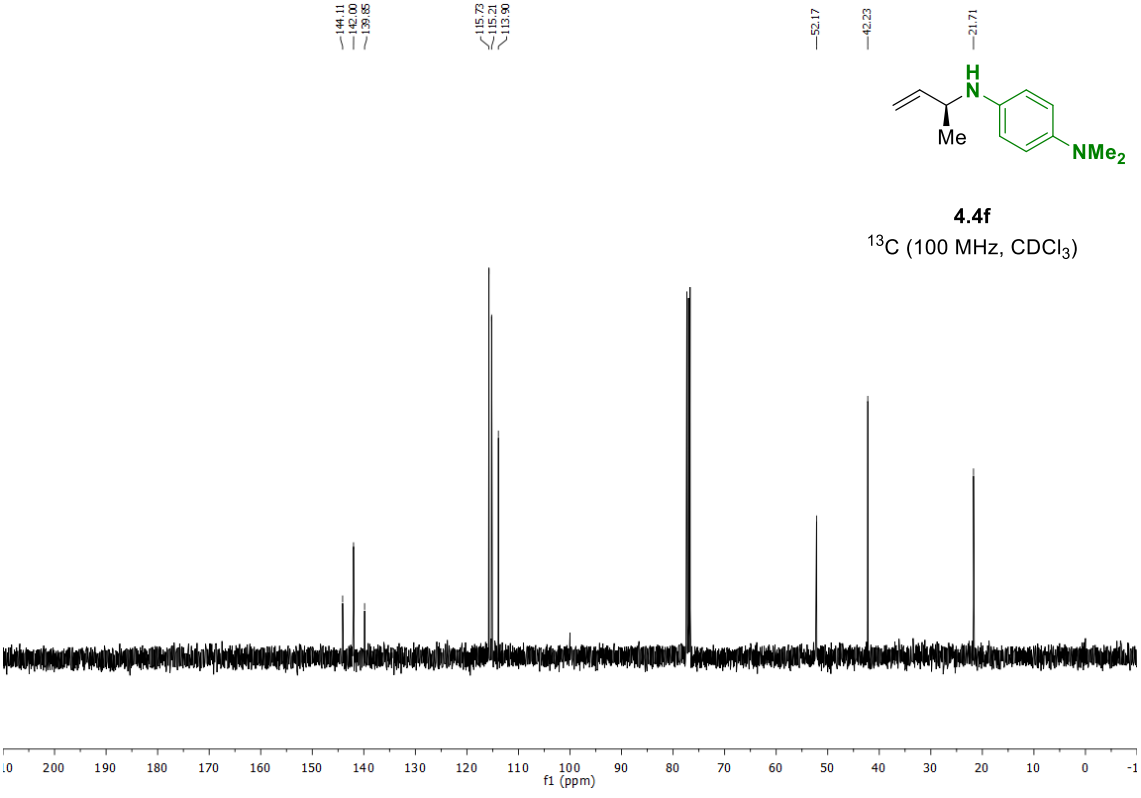
$[\alpha]_D^{28}$= –26.3 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 97:3, 1.00 mL/min, 254 nm), *ee* = 90%.



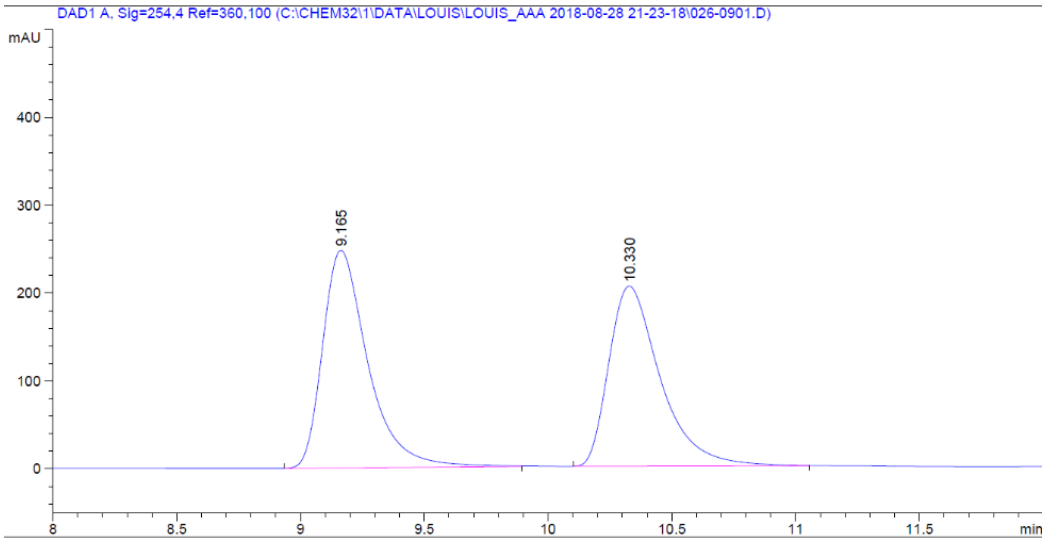
4.4f

^{1}H (400 MHz, $CDCl_3$)

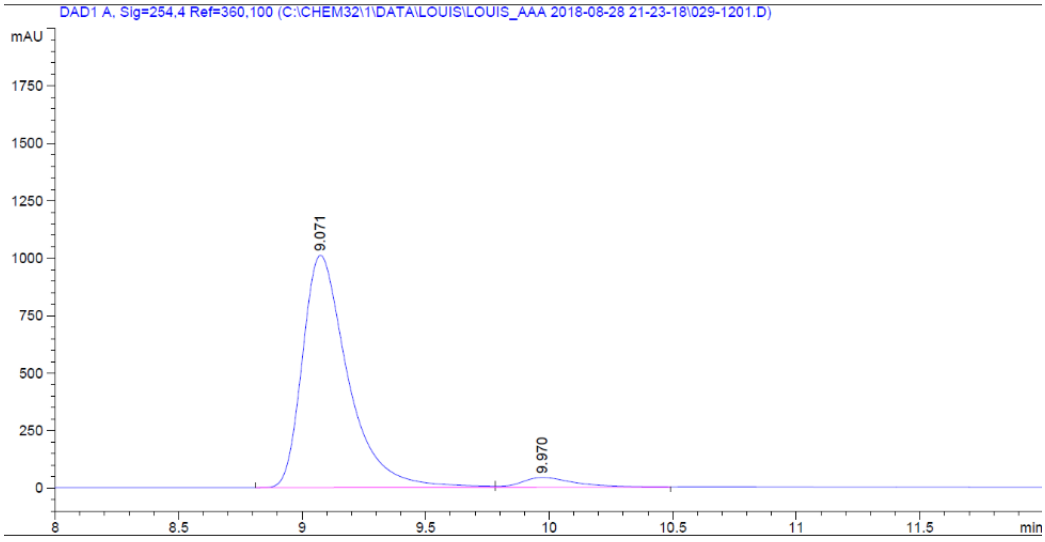


4.4f

^{13}C (100 MHz, $CDCl_3$)

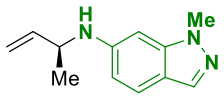


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.165	BB	0.1925	3157.57959	248.03835	51.5715
2	10.330	BB	0.2187	2965.14429	205.01358	48.4285



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.071	BV	0.1917	1.29836e4	1011.83209	95.0162
2	9.970	VB	0.2304	681.02032	43.55310	4.9838

(*S*)-N-(but-3-en-2-yl)-1-methyl-1H-indazol-6-amine (4.4g)



4.4g

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (129.5 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 30 hr). The title compound was obtained in 81% yield (71.7 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 30% over 20 min).

TLC (SiO_2) R_f = 0.38 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 1.0 Hz, 1H), 7.43 (dd, *J* = 8.6, 0.6 Hz, 1H), 6.49 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.33 (dt, *J* = 1.7, 0.8 Hz, 1H), 5.88 (ddd, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.27 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.13 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.07 (dtd, *J* = 8.1, 6.7, 5.2 Hz, 1H), 3.93 (s, 3H), 3.91 – 3.82 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 3H).

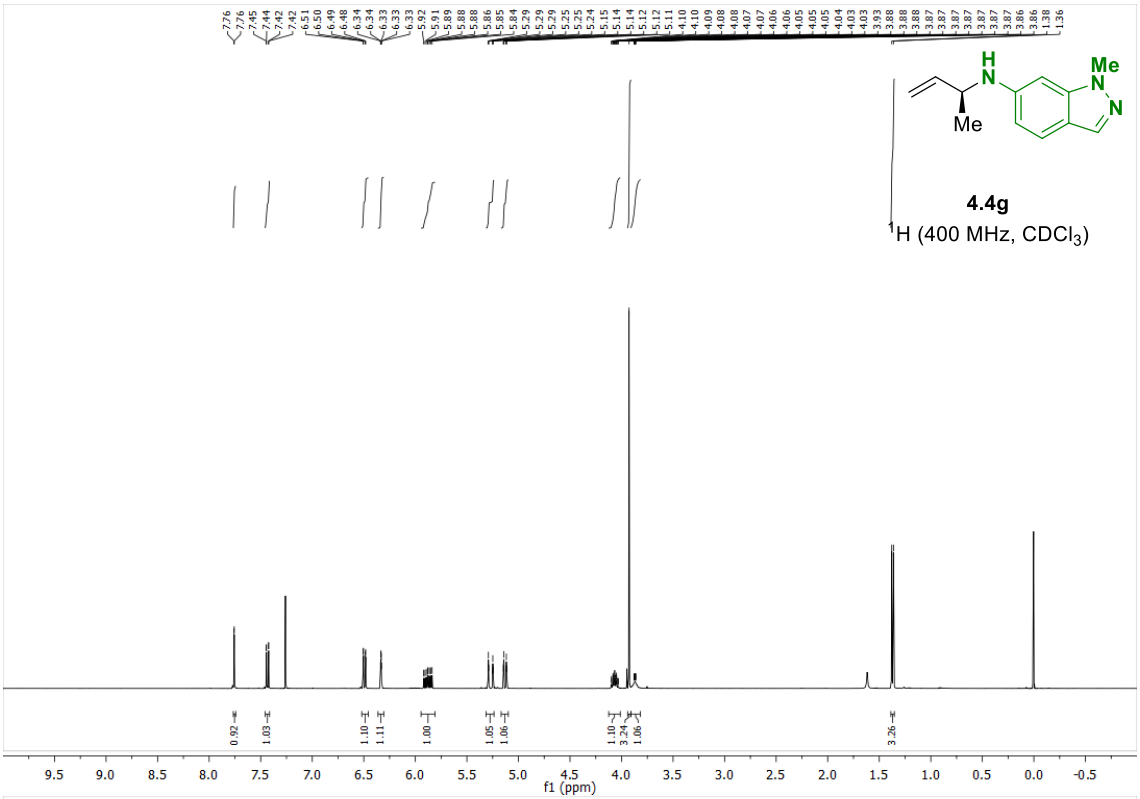
^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 141.8, 140.8, 132.6, 121.5, 117.0, 114.3, 112.4, 88.6, 51.3, 35.2, 21.6.

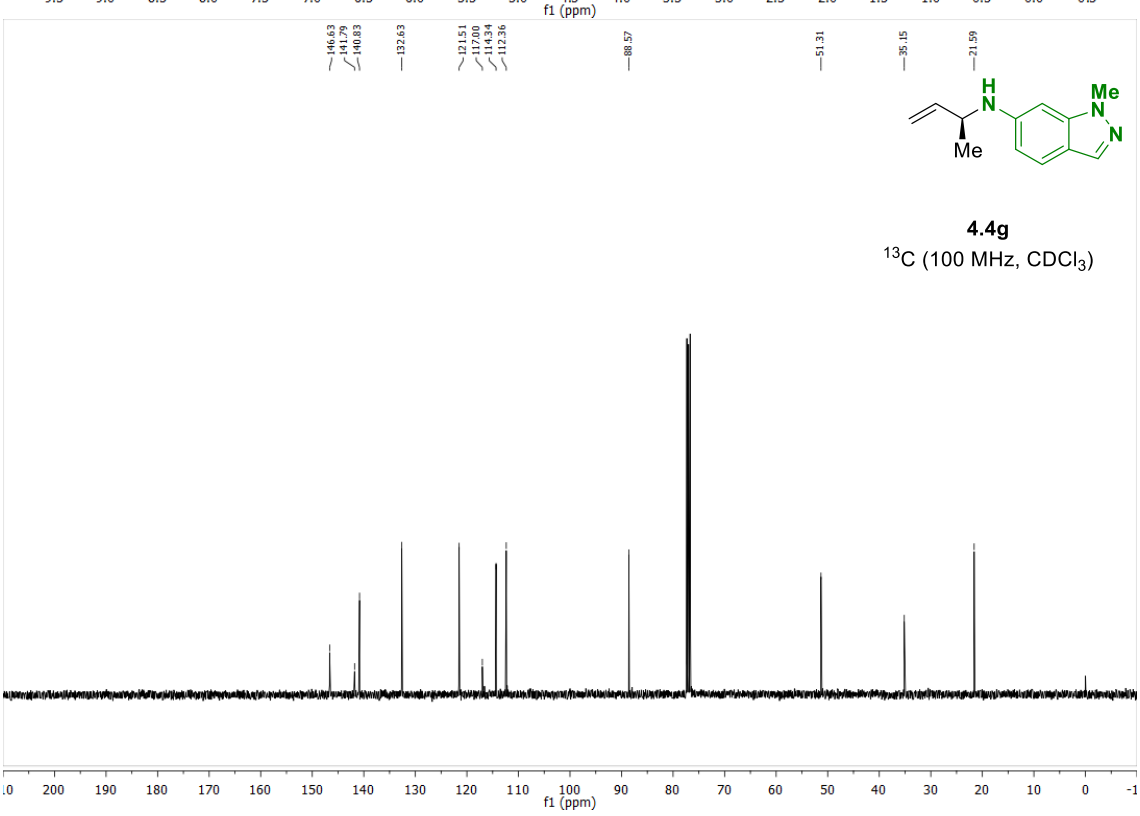
HRMS (ESI): Calculated for $C_{12}H_{15}N_3$ [M+H$^+$] = 202.1339, Found 202.1339.

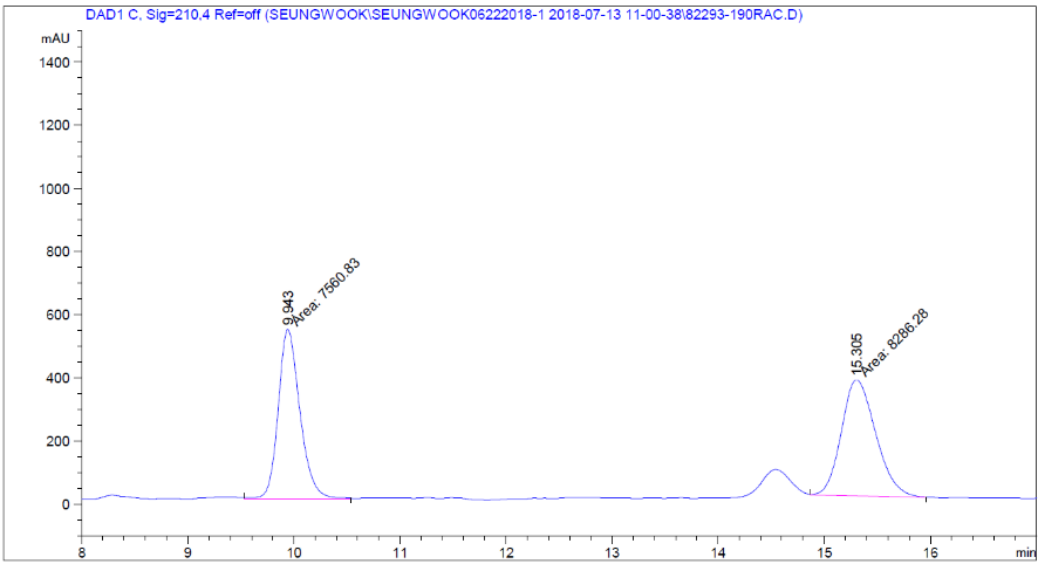
FTIR (neat): 3312, 2973, 1624, 1492, 1254, 1098, 982, 919, 732, 620 cm^{-1}.

$[\alpha]_D^{28}$= –60.3 (*c* 0.2, $CHCl_3$).

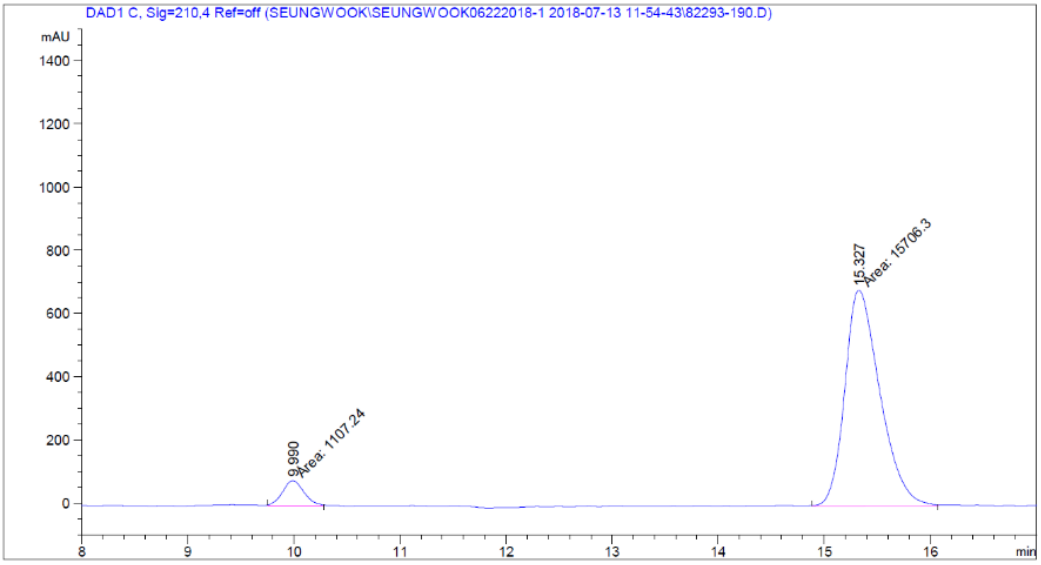
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 90:10, 1.00 mL/min, 210 nm), *ee* = 87%.


Me
N
N
H
N
Me
4.4g
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


Me
N
N
H
N
Me
4.4g
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

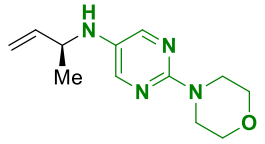


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.943	MM	0.2355	7560.83301	535.11896	47.7111
2	15.305	MM	0.3755	8286.28027	367.83386	52.2889



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.990	MM	0.2335	1107.24475	79.04131	6.5854
2	15.327	MM	0.3831	1.57063e4	683.38605	93.4146

(*S*)-N-(but-3-en-2-yl)-2-morpholinopyrimidin-5-amine (4.4h)



4.4h

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (158.6 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 82% yield (84.5 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 80% over 20 min).

TLC (SiO_2) R_f = 0.37 (hexanes: ethyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 2H), 5.76 (ddd, *J* = 17.2, 10.3, 6.2 Hz, 1H), 5.18 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.11 (dt, *J* = 10.3, 1.2 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.79 – 3.76 (m, 4H), 3.63 (dd, *J* = 5.7, 4.0 Hz, 4H), 1.31 (d, *J* = 6.6 Hz, 3H).

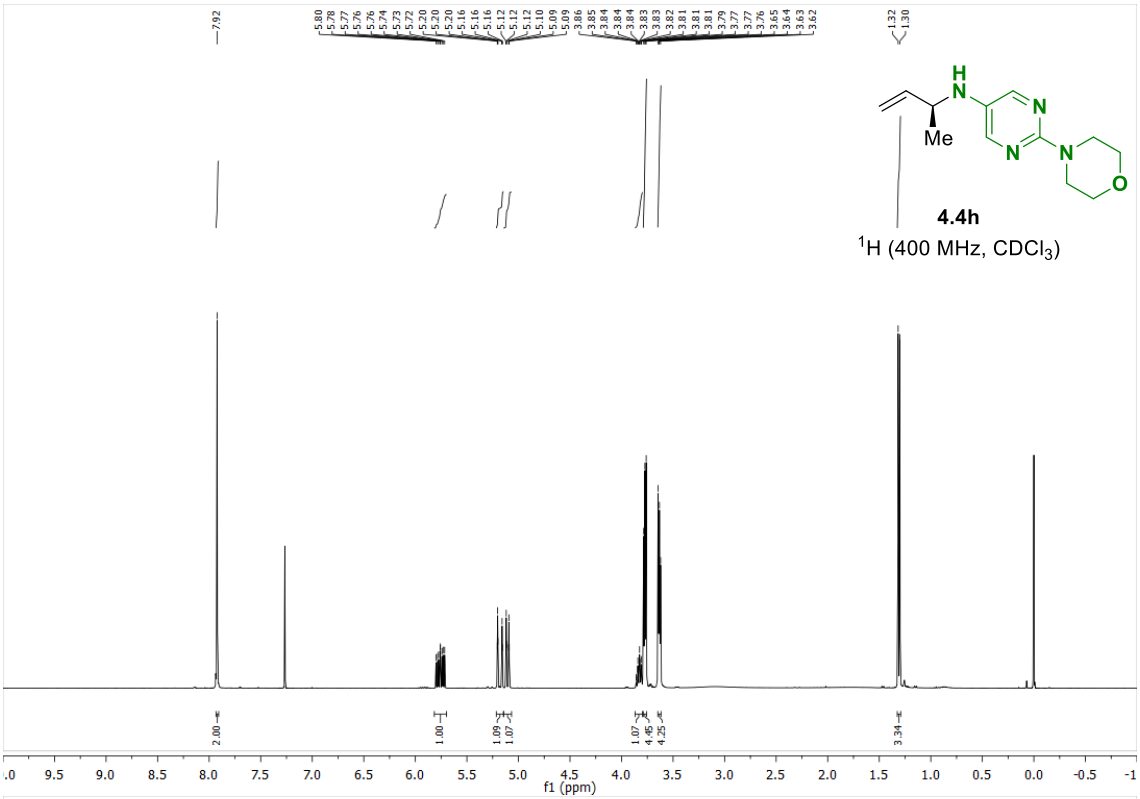
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 145.2, 140.6, 133.4, 115.1, 66.9, 52.8, 45.2, 21.7.

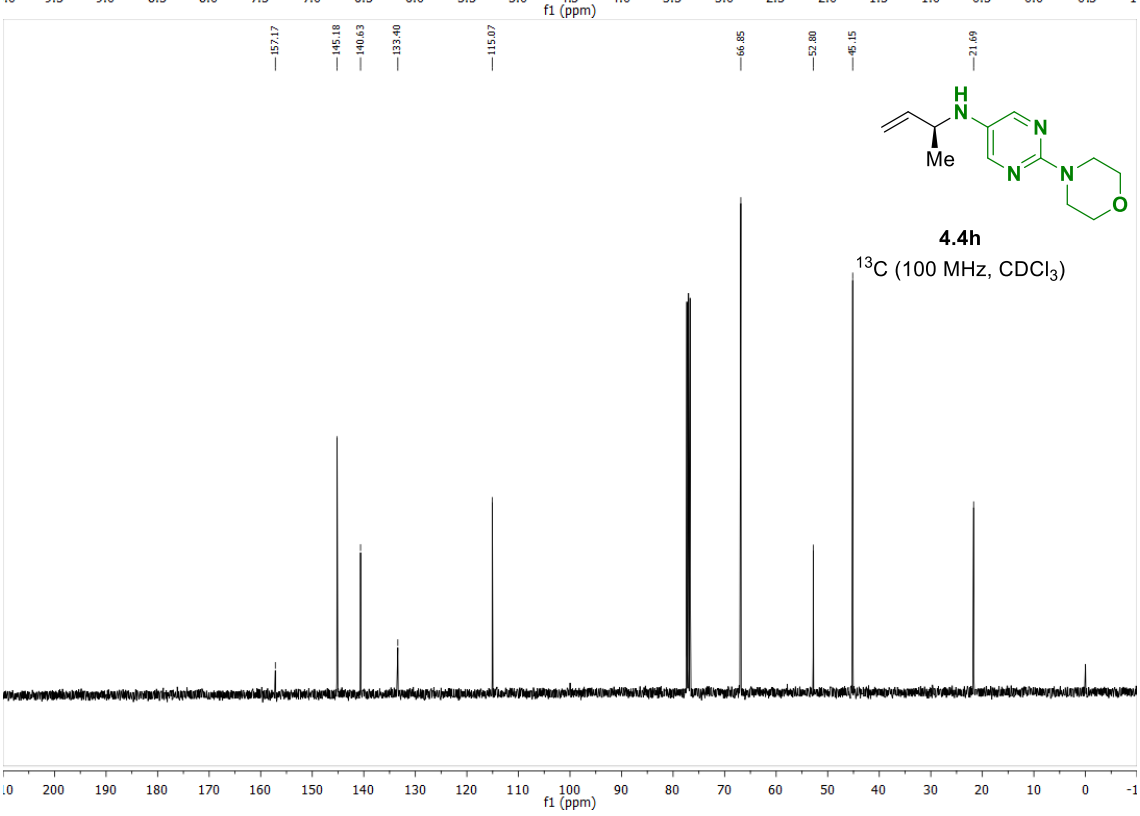
HRMS (ESI): Calculated for $C_{12}H_{18}N_4O$ [M+H$^+$] = 235.1553, Found 235.1555.

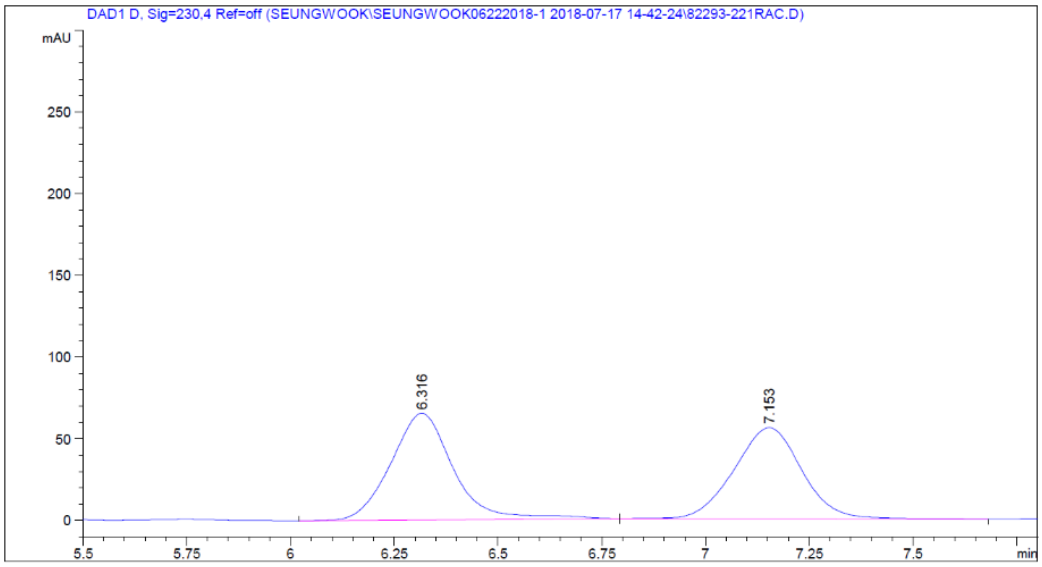
FTIR (neat): 2968, 1480, 1444, 1264, 1116, 954, 731 cm^{-1}.

$[\alpha]_D^{28}$= +9.92 (*c* 1.0, $CHCl_3$).

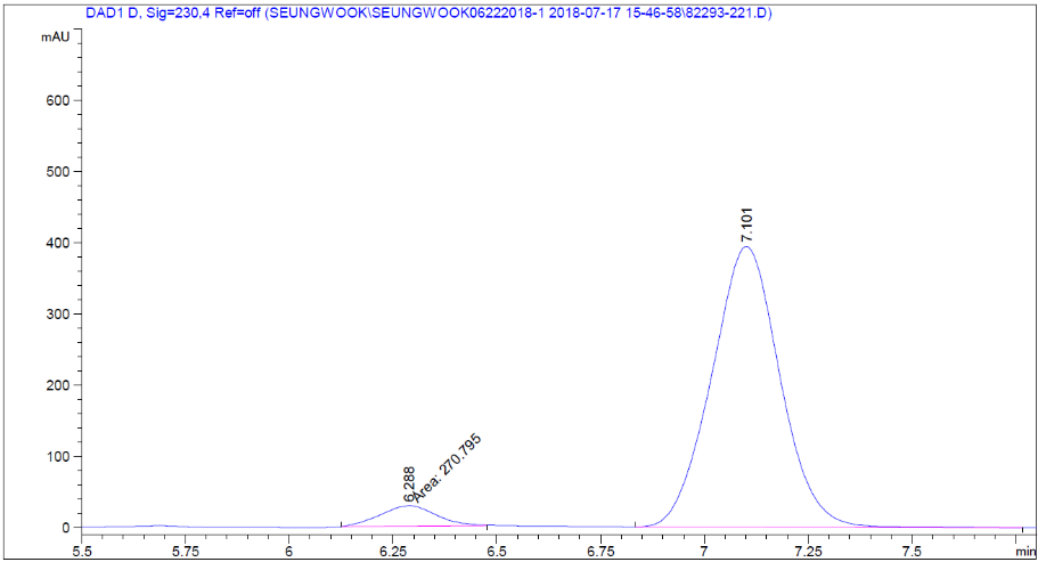
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 85:15, 1.00 mL/min, 230 nm), *ee* = 89%.


Me
4.4h
1H (400 MHz, CDCl3)
f1 (ppm)


Me
4.4h
13C (100 MHz, CDCl3)
f1 (ppm)

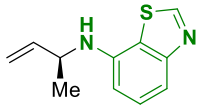


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.316	BB	0.1542	685.04590	65.40804	51.8899
2	7.153	BB	0.1726	635.14404	55.87535	48.1101



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.288	MM	0.1566	270.79501	28.82882	5.6630
2	7.101	BB	0.1734	4511.04883	394.44131	94.3370

(*S*)-N-(but-3-en-2-yl)benzo[d]thiazol-7-amine (4.4i)



4.4i

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (132.2 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 30 hr). The title compound was obtained in 81% yield (72.8 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 30% over 20 min).

TLC (SiO_2) R_f = 0.52 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.57 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 5.90 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.26 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.13 (dt, *J* = 10.3, 1.3 Hz, 1H), 4.20 (dtd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 3.60 (d, *J* = 6.7 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H).

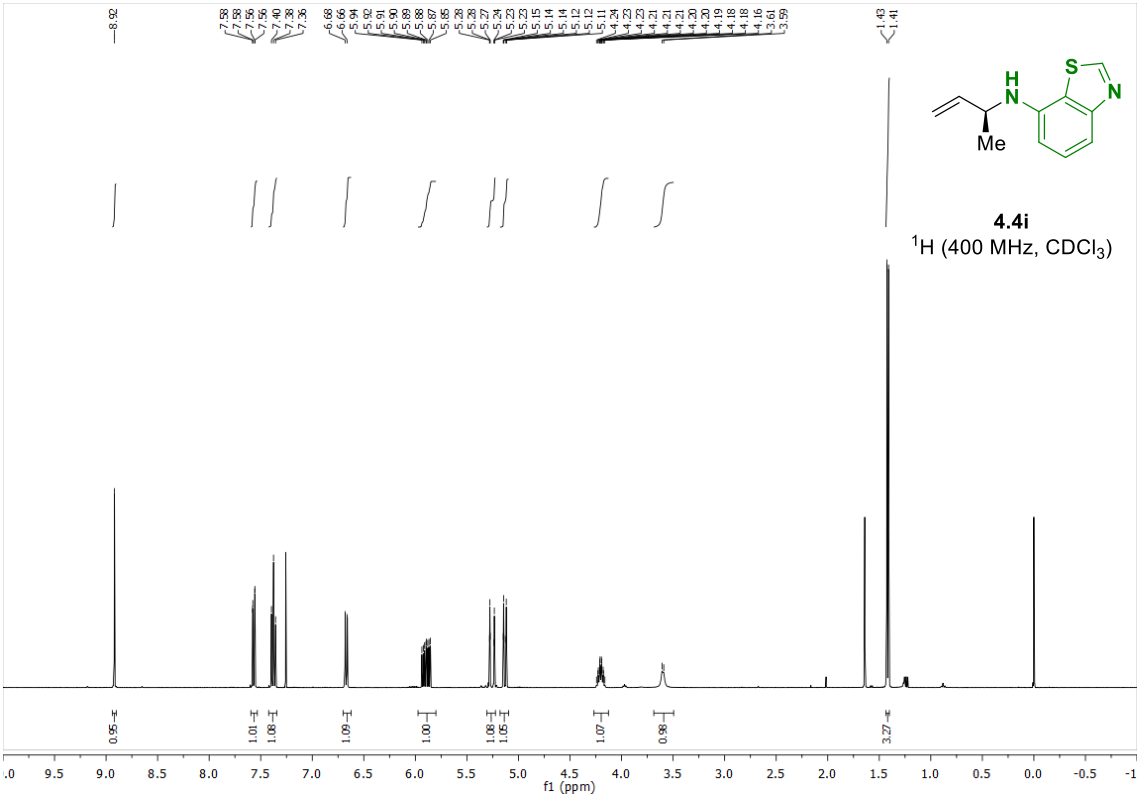
^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 151.9, 142.0, 140.5, 127.3, 120.5, 114.6, 113.3, 107.1, 51.6, 21.7.

HRMS (ESI): Calculated for $C_{11}H_{12}N_2S$ [M+H$^+$] = 205.0794, Found 205.0802.

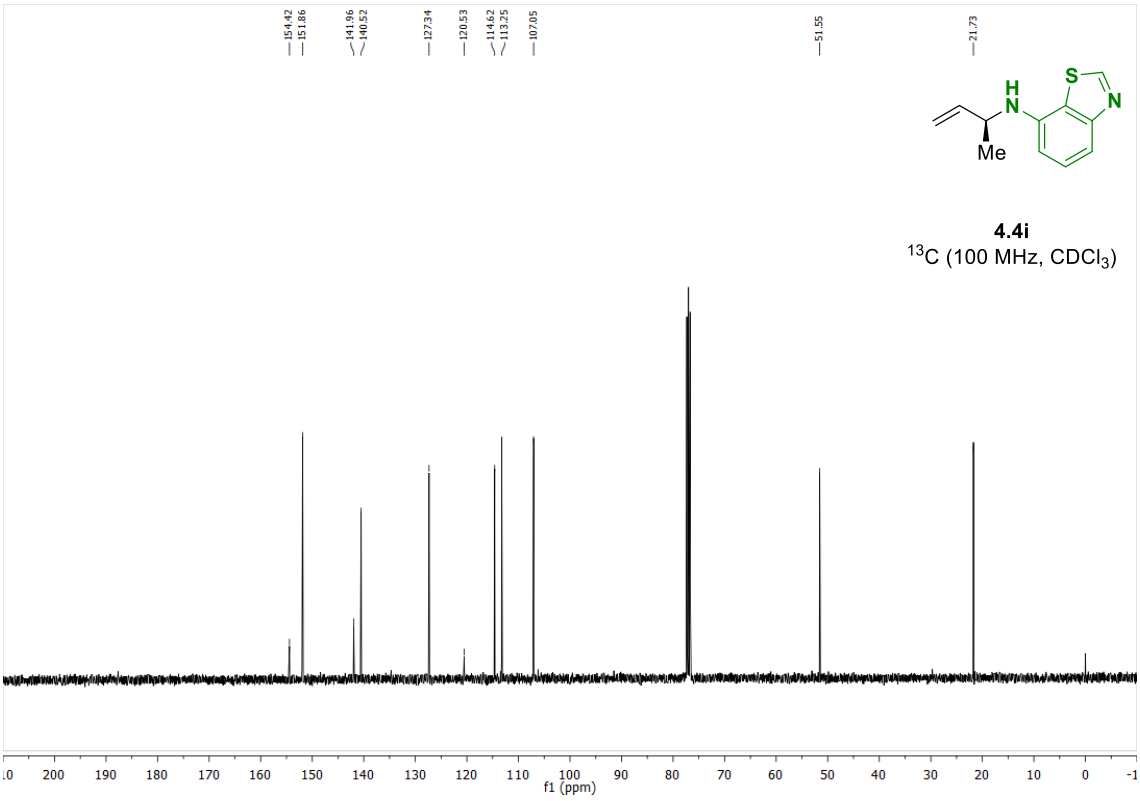
FTIR (neat): 3292, 2974, 1575, 1472, 1287, 1145, 1049, 920, 774, 717 cm^{-1}.

$[\alpha]_D^{28}$= +31.68 (*c* 0.2, $CHCl_3$).

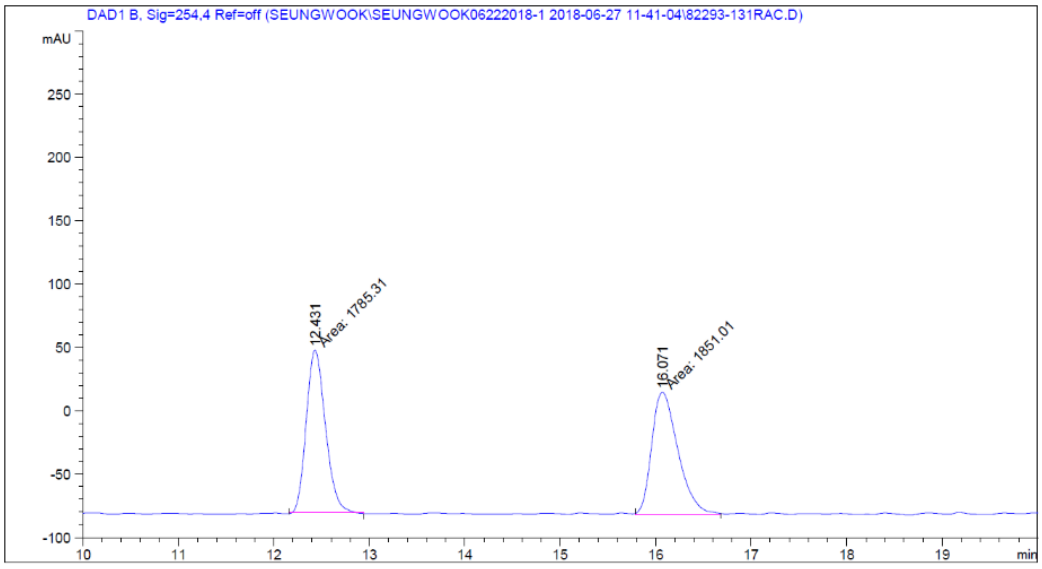
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 97.5:2.5, 1.00 mL/min, 254 nm), *ee* = 90%.



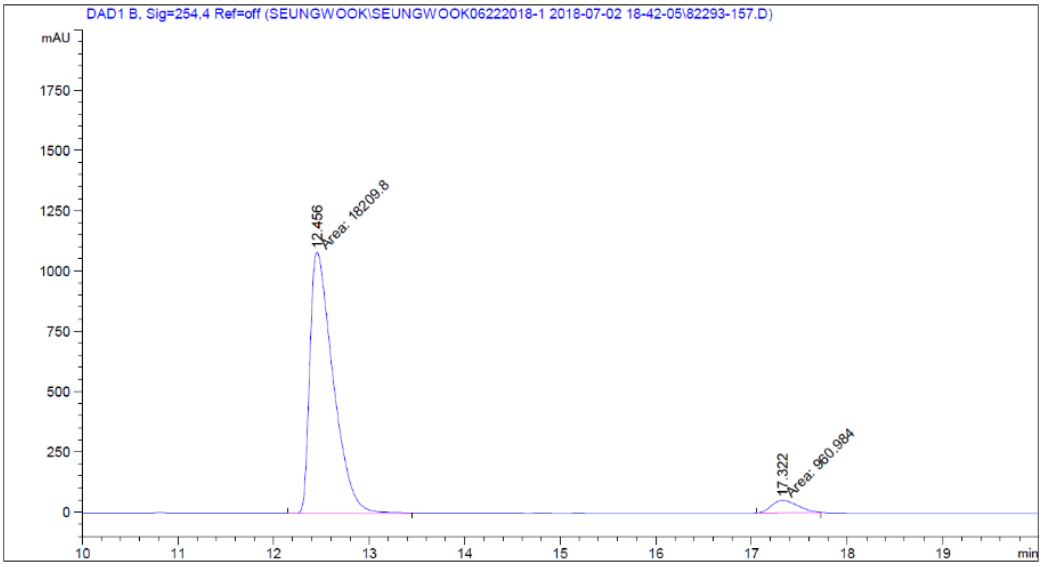
4.4i
^{1}H (400 MHz, $CDCl_3$)



4.4i
^{13}C (100 MHz, $CDCl_3$)

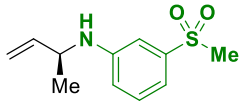


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.431	MM	0.2323	1785.31116	128.06386	49.0967
2	16.071	MM	0.3197	1851.00720	96.50237	50.9033



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.456	MM	0.2805	1.82098e4	1082.00134	94.9872
2	17.322	MM	0.3134	960.98425	51.09868	5.0128

(*S*)-N-(but-3-en-2-yl)-3-(methylsulfonyl)aniline (4.4j)



4.4j

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (150.7 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 40 hr). The title compound was obtained in 76% yield (75.3 mg, 0.33 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 10:1–4:1).

TLC (SiO_2) R_f = 0.41 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.9 Hz, 1H), 7.18 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 7.10 (t, *J* = 2.1 Hz, 1H), 6.84 – 6.74 (m, 1H), 5.79 (ddd, *J* = 17.0, 10.3, 5.4 Hz, 1H), 5.22 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.12 (dt, *J* = 10.3, 1.2 Hz, 1H), 4.13 – 3.90 (m, 2H), 3.01 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H).k

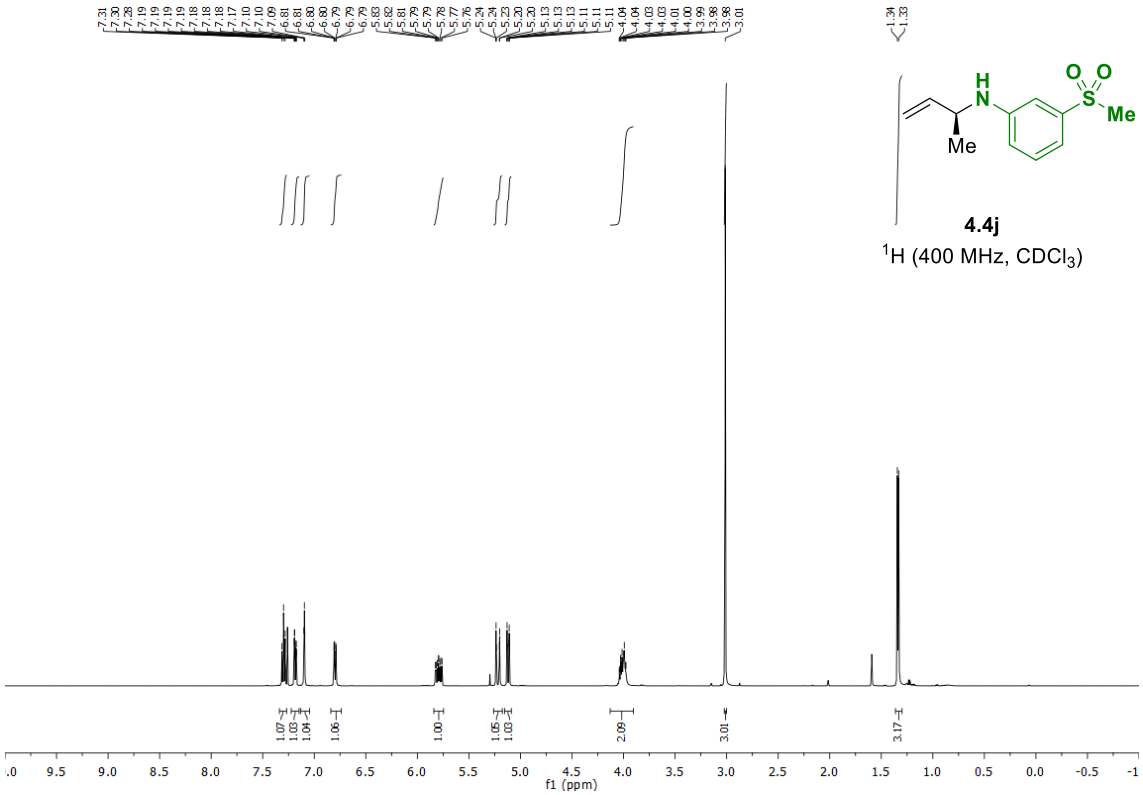
^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.0, 141.3, 140.0, 130.1, 118.0, 115.3, 114.8, 111.0, 51.0, 44.4, 21.5.

HRMS (ESI): Calculated for $C_{11}H_{15}NO_2S$ [M+H$^+$] = 226.0896, Found 226.0900.

FTIR (neat): 3379, 1599, 1487, 1296, 1141, 961, 757, 683 cm^{-1}.

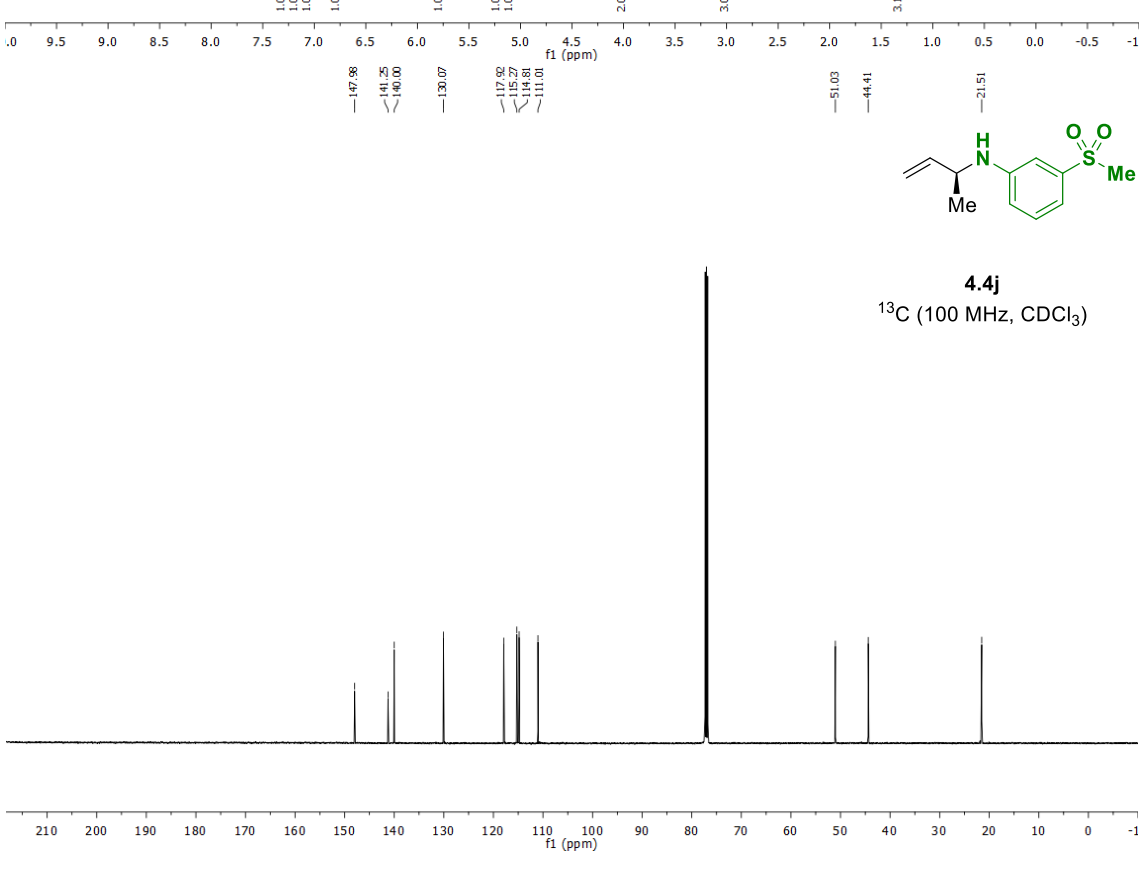
$[\alpha]_D^{28}$= –33.3 (*c* 1.0, $CHCl_3$).

HPLC (Two connected chiralcel AD-H column, hexanes:*i*-PrOH = 95:5, 1.00 mL/min, 254 nm), *ee* = 91%.



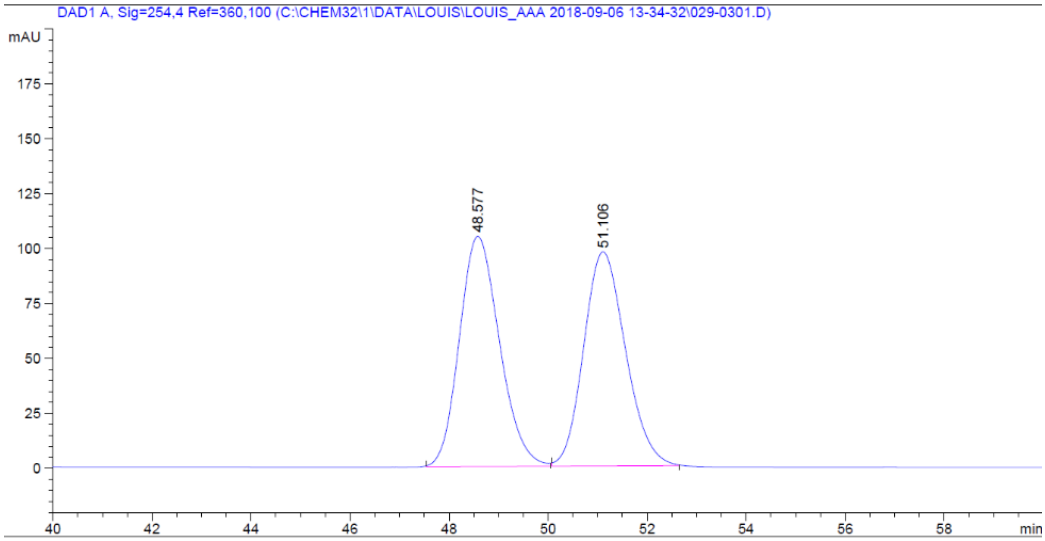
4.4j

^{1}H (400 MHz, $CDCl_3$)

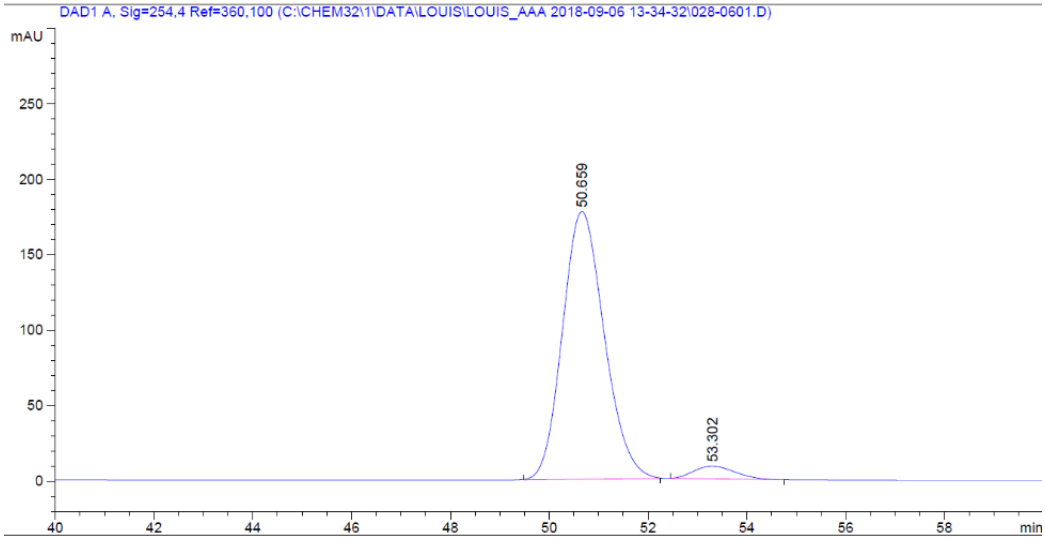


4.4j

^{13}C (100 MHz, $CDCl_3$)

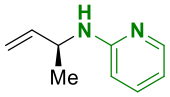


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.577	BB	0.8665	5887.28076	104.62562	50.7171
2	51.106	BB	0.8990	5720.79297	97.43137	49.2829



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.659	BB	0.9036	1.04261e4	177.42329	95.5102
2	53.302	BB	0.7200	490.10962	8.48417	4.4898

(*S*)-N-(but-3-en-2-yl)pyridin-2-amine (4.4k)



4.4k

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (82.8 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 74% yield (48.3 mg, 0.33 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 10:1–4:1).

TLC (SiO_2) R_f = 0.45 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.40 (ddd, *J* = 8.8, 7.1, 1.9 Hz, 1H), 6.56 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.36 (dt, *J* = 8.4, 1.0 Hz, 1H), 5.87 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.08 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.48 (br, 1H), 4.32 – 4.20 (m, 1H), 1.33 (d, *J* = 6.7 Hz, 3H).

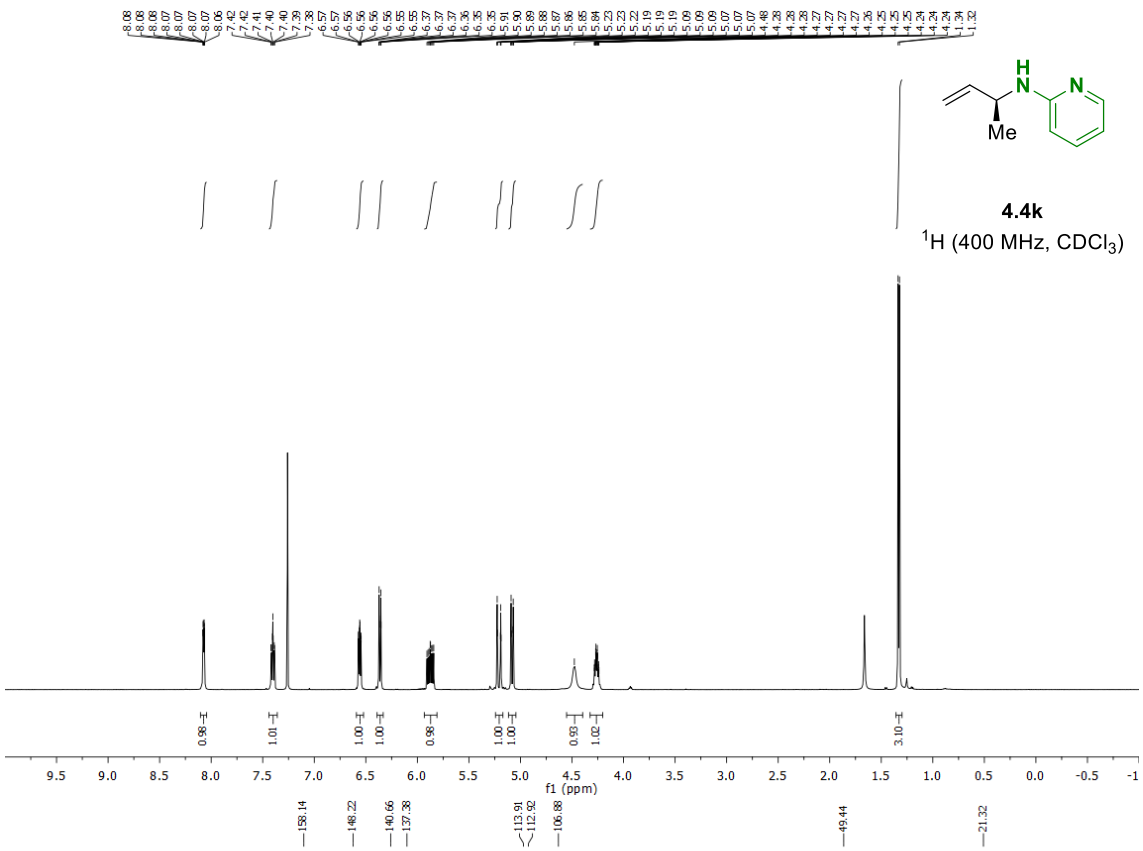
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1, 148.2, 140.7, 137.4, 113.9, 112.9, 106.9, 49.4, 21.3.

HRMS (ESI): Calculated for $C_9H_{12}N_2$ [M+H$^+$] = 149.1073, Found 149.1073.

FTIR (neat): 3528, 2974, 1599, 1445, 1330, 1154, 987, 920, 751 cm^{-1}.

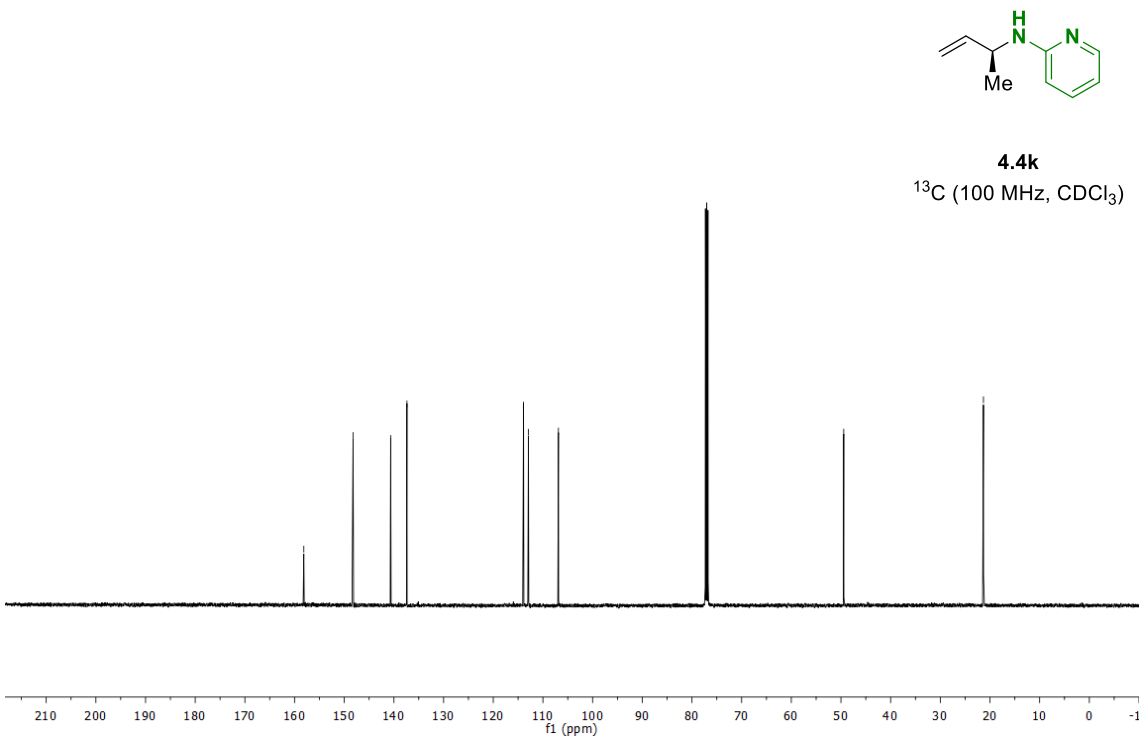
$[\alpha]_D^{28}$= +6.3 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel OD-3 column, hexanes:*i*-PrOH = 90:10, 1.00 mL/min, 210 nm), *ee* = 91%.



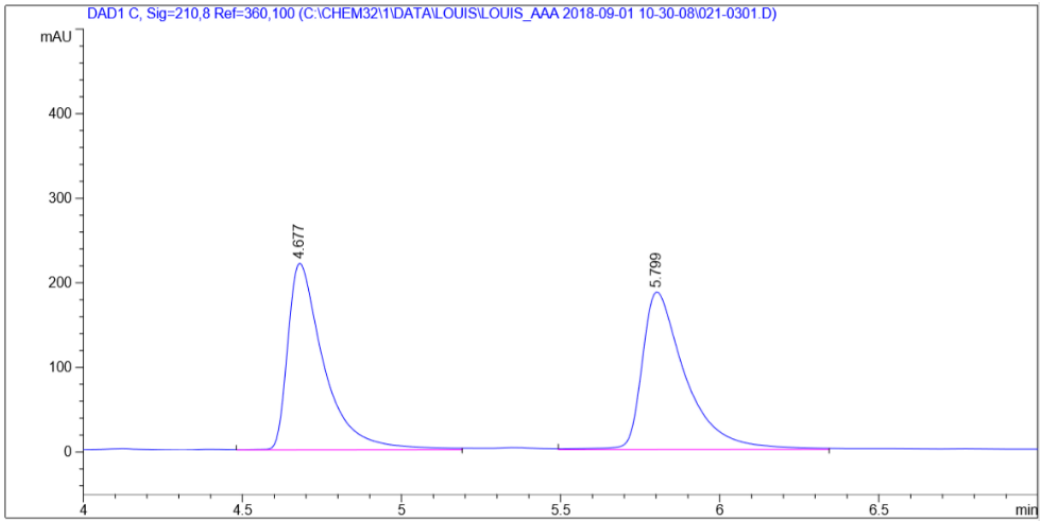
4.4k

^{1}H (400 MHz, $CDCl_3$)

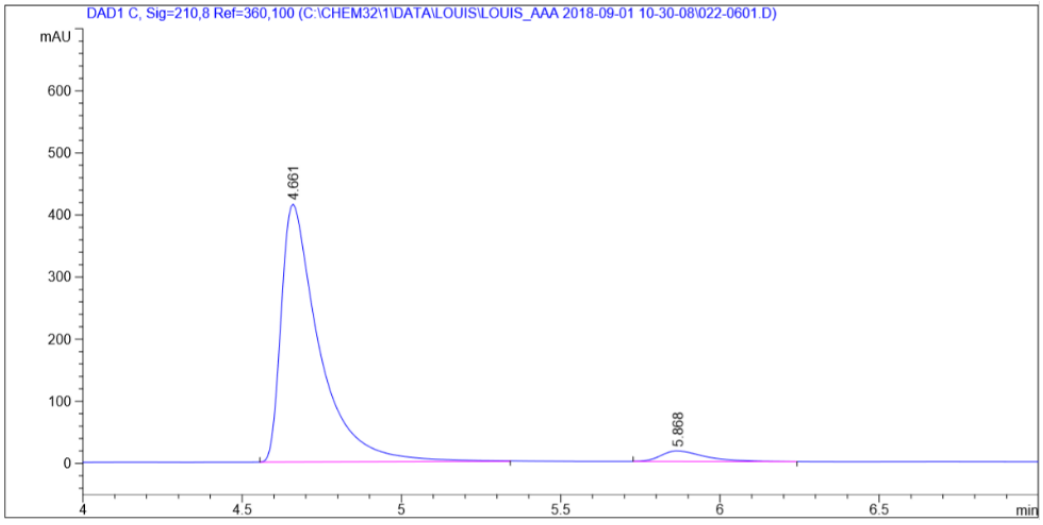


4.4k

^{13}C (100 MHz, $CDCl_3$)

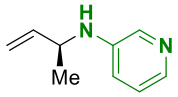


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.677	VB	0.1161	1744.52979	221.07109	49.5692
2	5.799	VB	0.1390	1774.85303	186.55690	50.4308



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.661	BB	0.1185	3436.27466	415.40756	95.3755
2	5.868	BB	0.1433	166.61571	17.15253	4.6245

(*S*)-N-(but-3-en-2-yl)pyridin-3-amine (4.4l)



4.4l

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (82.8 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 30 hr). The title compound was obtained in 87% yield (56.7 mg, 0.38 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 50% over 20 min).

TLC (SiO_2) R_f = 0.22 (hexanes: ethyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.93 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.05 (ddd, *J* = 8.3, 4.7, 0.7 Hz, 1H), 6.86 (ddd, *J* = 8.3, 2.9, 1.4 Hz, 1H), 5.80 (ddd, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.11 (dt, *J* = 10.4, 1.3 Hz, 1H), 3.97 (s, 1H), 3.69 (br, 1H), 1.34 (d, *J* = 6.7 Hz, 3H).

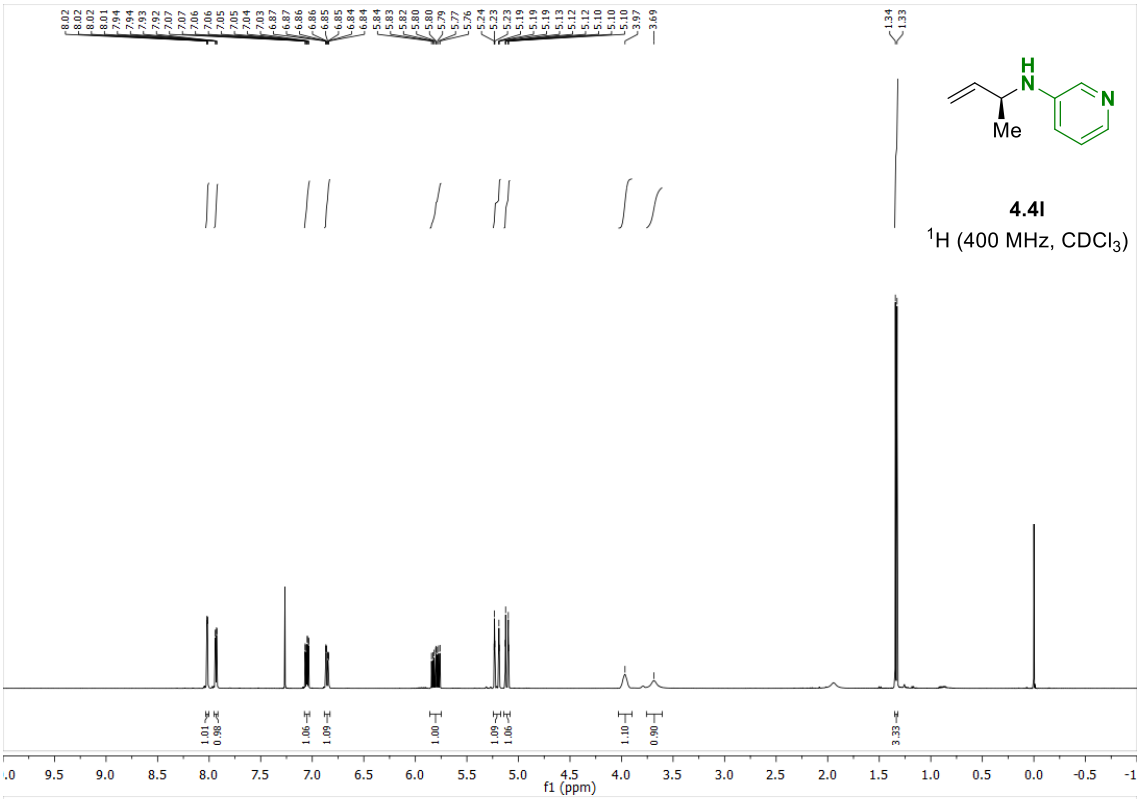
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 140.3, 138.7, 136.6, 123.6, 119.1, 114.7, 51.0, 21.6.

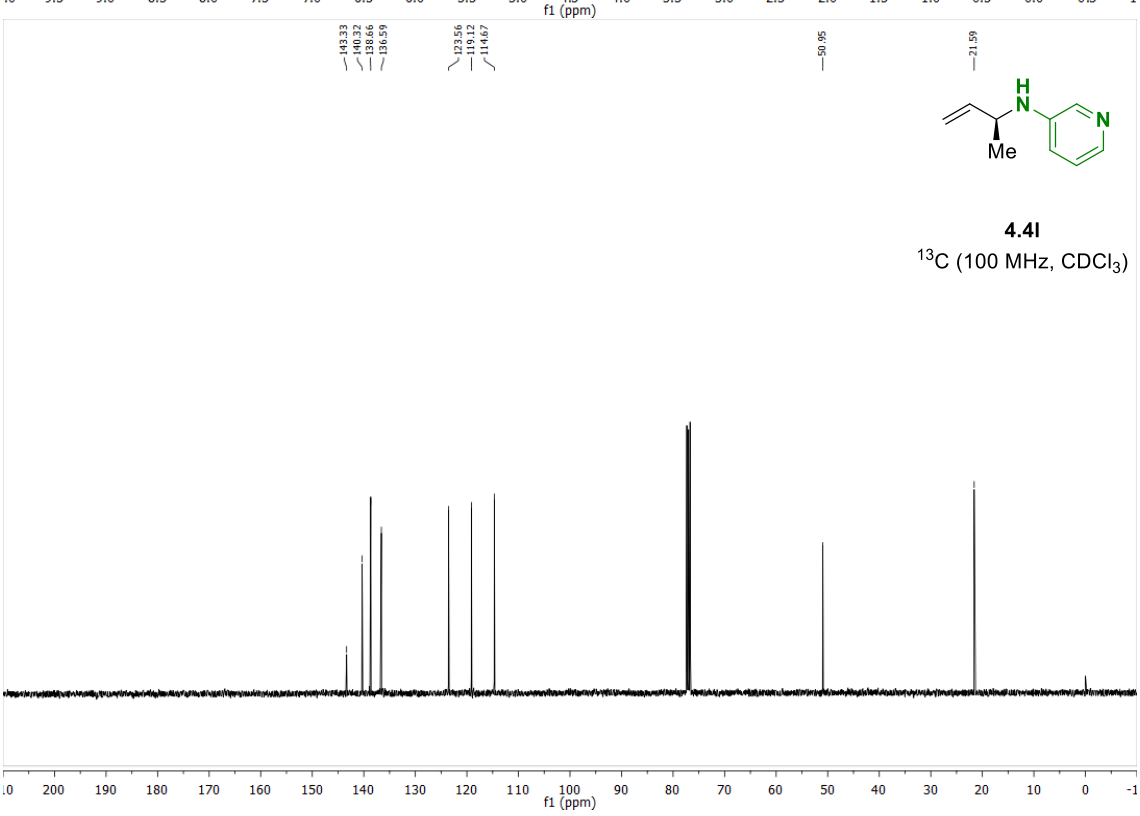
HRMS (ESI): Calculated for $C_9H_{12}N_2$ [M+H$^+$] = 149.1073, Found 149.1075.

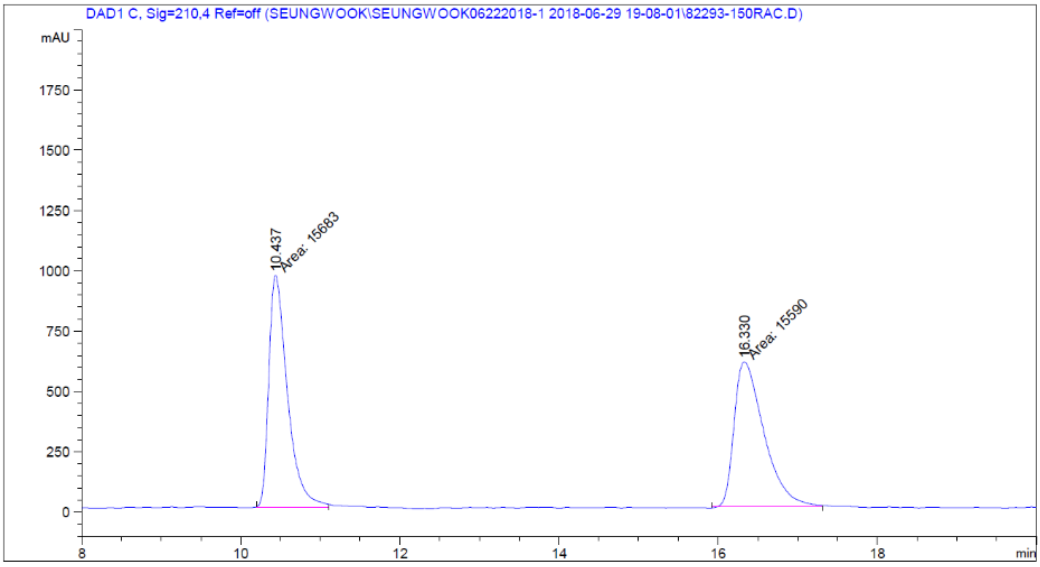
FTIR (neat): 3253, 2973, 1578, 1481, 1414, 1241, 991, 917, 791, 706 cm^{-1}.

$[\alpha]_D^{28}$= –12.7 (*c* 0.2, $CHCl_3$).

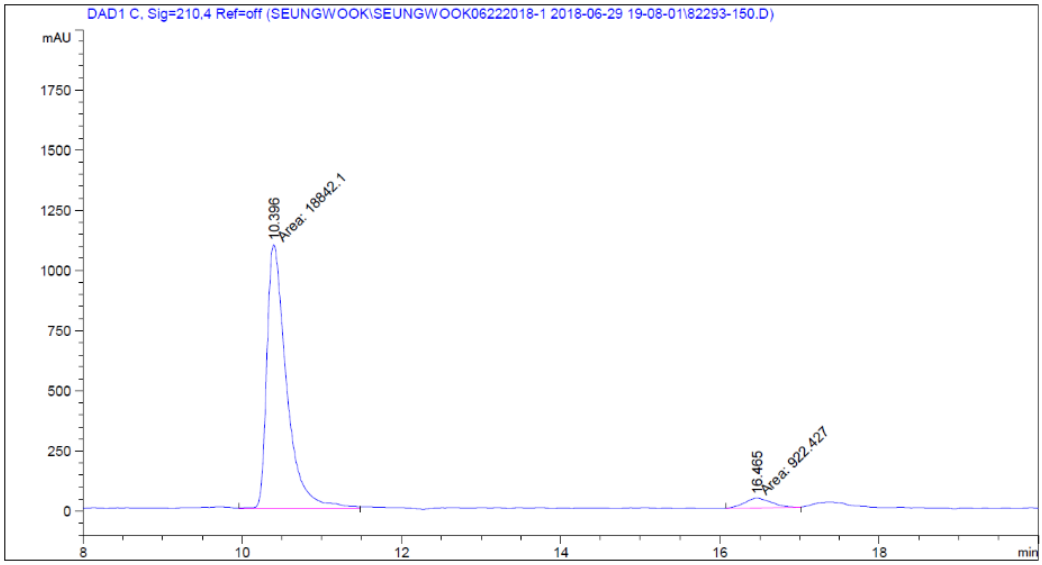
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 90:10, 1.00 mL/min, 210 nm), *ee* = 91%.


8.02
8.02
8.02
8.01
8.01
7.94
7.93
7.92
7.07
7.07
7.06
7.06
7.05
7.05
7.04
7.03
6.87
6.87
6.86
6.86
6.85
6.85
6.84
6.84
5.84
5.83
5.82
5.80
5.80
5.79
5.77
5.76
5.24
5.23
5.23
5.19
5.19
5.19
5.13
5.12
5.12
5.10
5.10
3.97
3.69
1.34
1.33
H
N
N
Me
4.4l
1H (400 MHz, CDCl3)
1.01
0.98
1.06
1.09
1.00
1.09
1.06
1.10
0.90
3.33
f1 (ppm)


143.33
140.32
138.66
136.59
123.56
119.12
114.67
50.95
21.59
H
N
N
Me
4.4l
13C (100 MHz, CDCl3)
f1 (ppm)

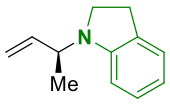


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.437	MM	0.2717	1.56830e4	962.08154	50.1488
2	16.330	MM	0.4339	1.55900e4	598.80670	49.8512



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.396	MM	0.2865	1.88421e4	1096.21130	95.3329
2	16.465	MM	0.3773	922.42676	40.75188	4.6671

(*S*)-1-(but-3-en-2-yl)indoline (4.5a)



4.5a

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (104.9 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 92% yield (70.1 mg, 0.40 mmol) as a light purple oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 10 min).

TLC (SiO_2) R_f = 0.49 (heptane: isopropyl acetate = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10-7.02 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.94 (ddd, *J* = 17.5, 10.5, 5.3 Hz, 1H), 5.26-5.15 (m, 2H), 4.22 (qd, *J* = 6.9, 5.1 Hz, 1H), 3.44-3.30 (m, 2H), 2.96 (t, *J* =18.5 Hz, 2H), 1.32 (d, *J* = 6.8 Hz, 3H).

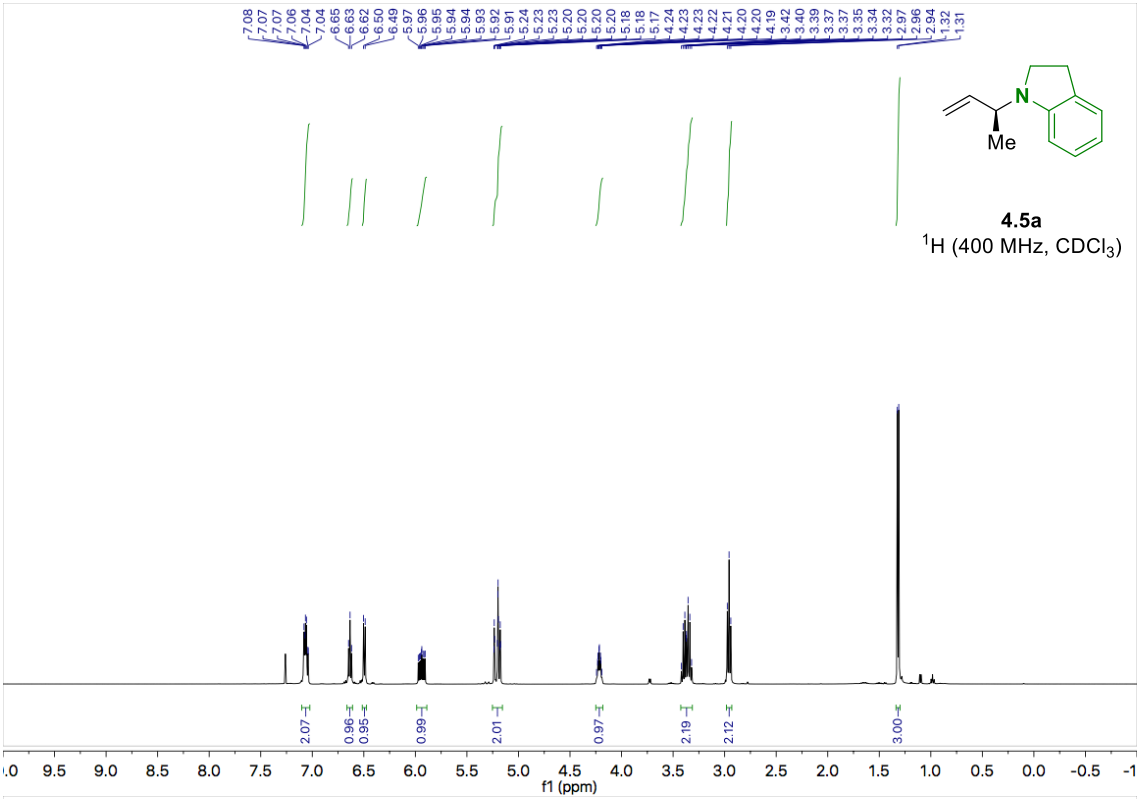
^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 138.4, 130.3, 127.2, 124.4, 117.2, 115.7, 107.6, 52.6, 47.1, 28.2, 15.5.

HRMS (ESI): Calculated for $C_{12}H_{15}N$ $[M+H^+]$ = 174.1277, Found 174.1227.

FTIR (neat): 3047, 3024, 2973, 2933, 2845, 1606, 1487, 1473, 1458, 1257, 1185, 1023, 919, 743 cm^{-1}.

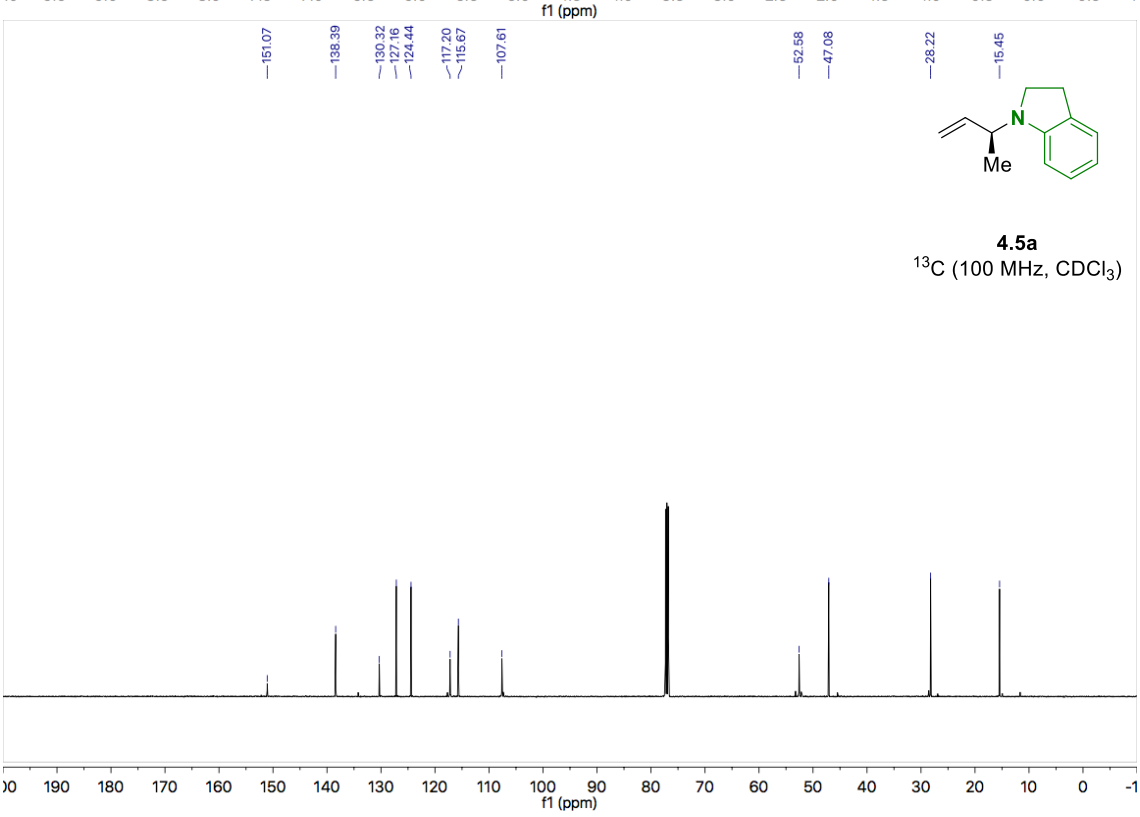
$[\alpha]_D^{28}$= -551.36 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 95:5, 1.00 mL/min, 254 nm), *ee* = 92%.



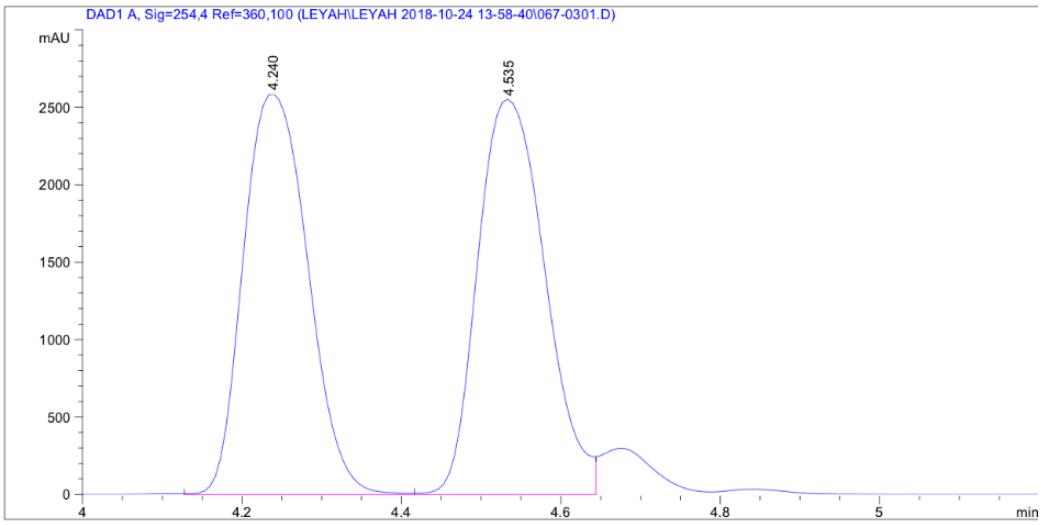
4.5a

^{1}H (400 MHz, $CDCl_3$)

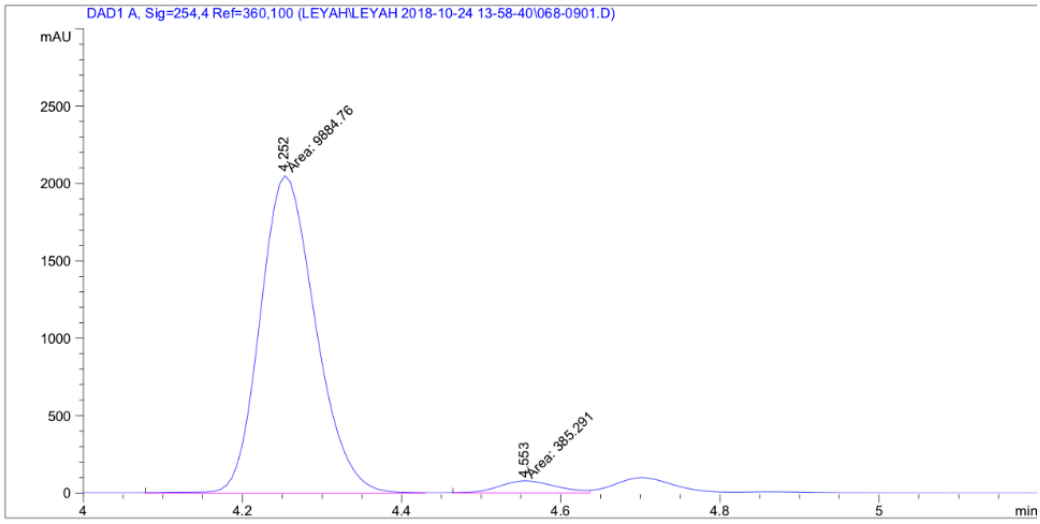


4.5a

^{13}C (100 MHz, $CDCl_3$)

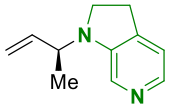


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.240	VV	0.0915	1.45323e4	2589.30933	49.2911
2	4.535	VV	0.0943	1.49503e4	2553.09814	50.7089



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.252	MM	0.0801	9884.76270	2055.56738	96.2484
2	4.553	MM	0.0827	385.29080	77.64413	3.7516

(*S*)-1-(but-3-en-2-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine (4.5b)



4.5b

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (105.7 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 78% yield (59.8 mg, 0.34 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 20% over 20min).

TLC (SiO_2) R_f = 0.25 (heptane: isopropyl acetate =1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 4.6 Hz, 1H), 7.80 (d, *J* = 0.9 Hz, 1H), 6.97 (dq, *J* = 4.6, 1.0 Hz, 1H), 5.88 (ddd, *J* = 17.4, 10.5, 5.5 Hz, 1H), 5.21 (dt, *J* = 12.2, 1.4 Hz, 1H), 5.18 (dt, *J* = 5.3, 1.4 Hz, 1H), 4.18 (qdt, *J* = 7.0, 5.5, 1.6 Hz, 1H), 3.45-3.32 (m, 2H), 2.98-2.91 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H).

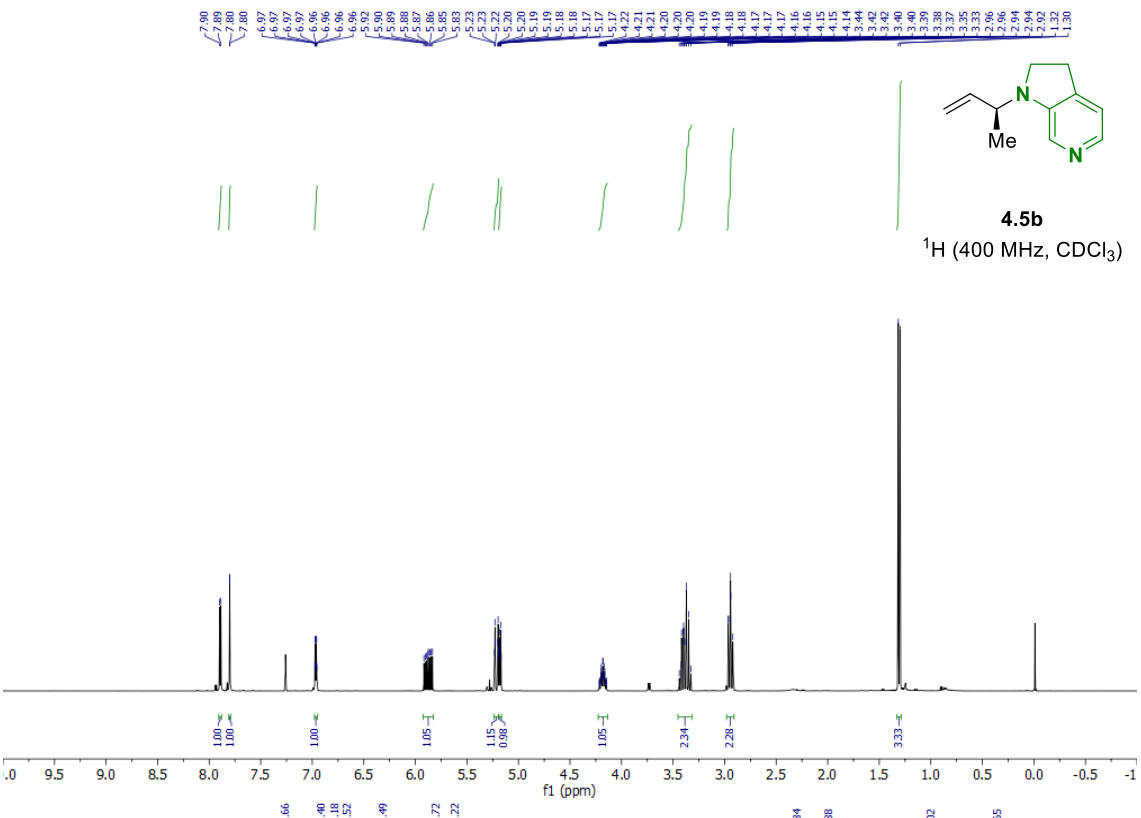
^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 139.4, 139.2, 137.5, 129.5, 119.7, 116.2, 52.8, 46.9, 28.0, 15.7.

HRMS (ESI): Calculated for $C_{11}H_{14}N_2$ $[M+H^+]$ =175.1230, Found 175.1226.

FTIR (neat): 3037, 2974, 2360, 2341, 1597, 1493, 1426, 129.4, 1183, 923, 819, 772, 669, 567 cm^{-1}.

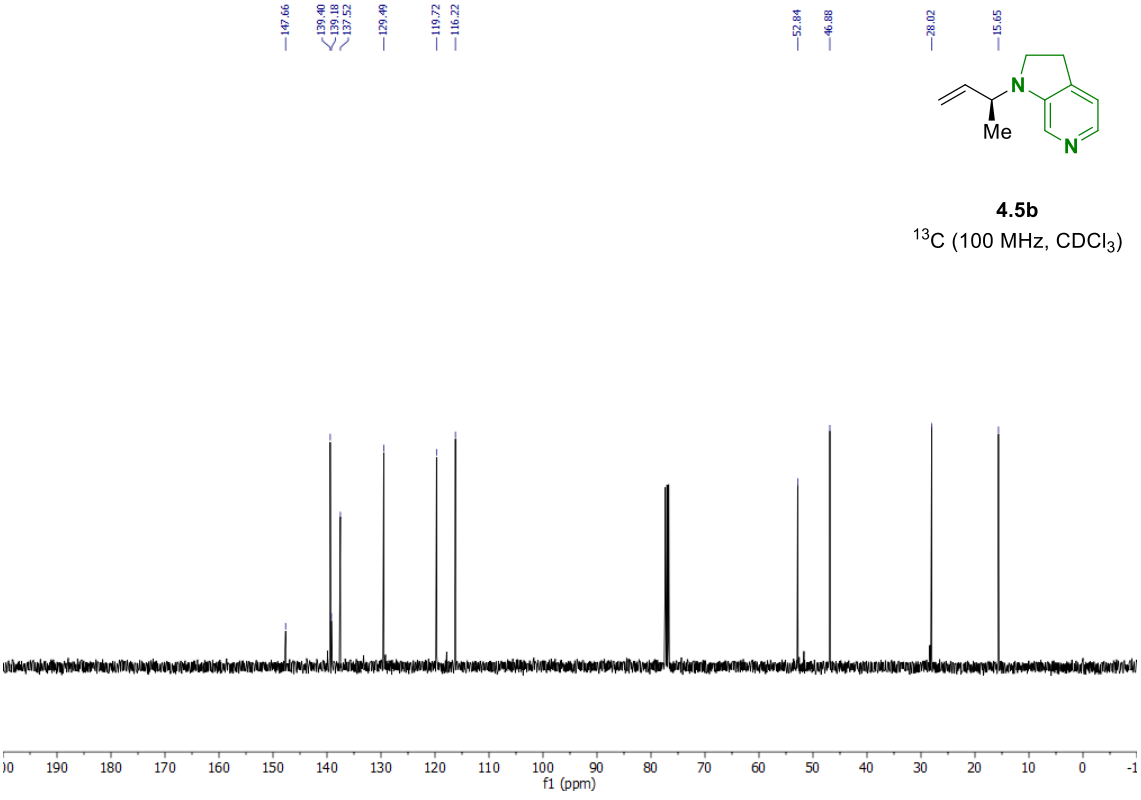
$[\alpha]_D^{28}$= –44.4 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 85:15, 1.00 mL/min, 254 nm), *ee* = 93%.



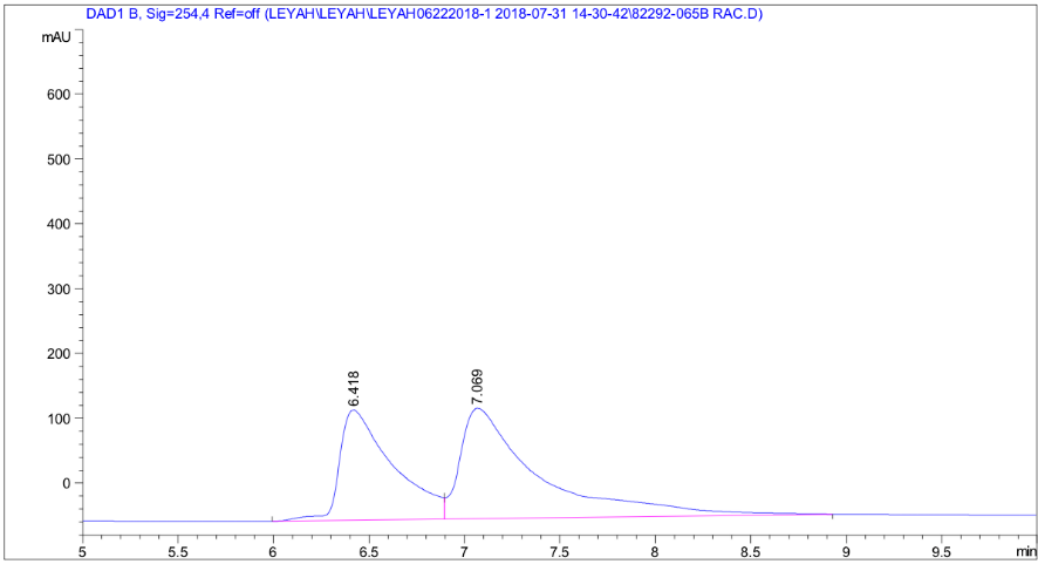
4.5b

^{1}H (400 MHz, $CDCl_3$)

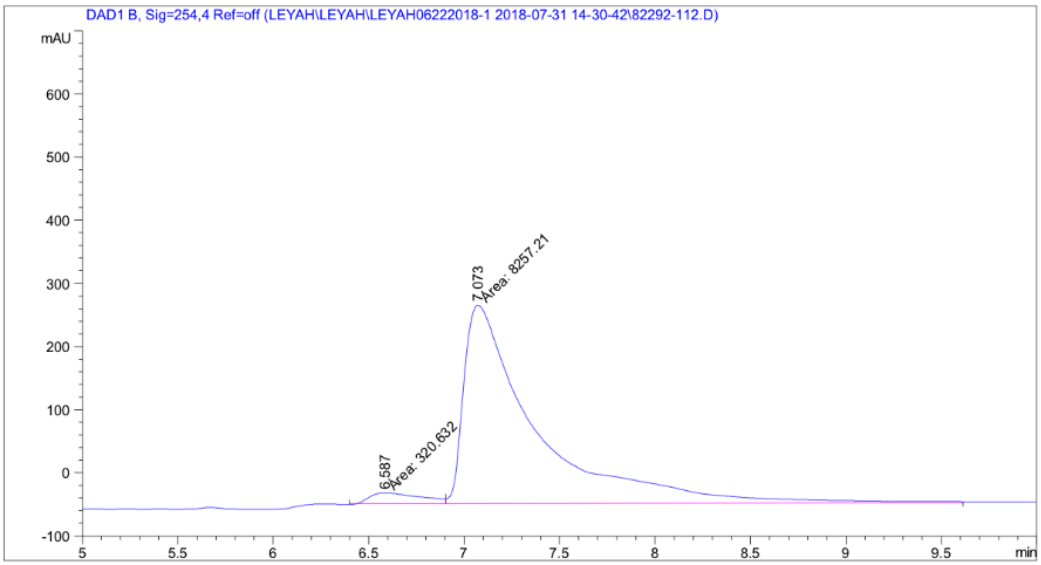


4.5b

^{13}C (100 MHz, $CDCl_3$)

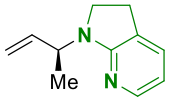


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.418	BV	0.2722	3296.05127	170.00136	40.7217
2	7.069	VB	0.3849	4798.03174	170.18459	59.2783



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.587	MF	0.3146	320.63168	16.98651	3.7379
2	7.073	FM	0.4379	8257.20508	314.27136	96.2621

(*S*)-1-(but-3-en-2-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (4.5c)



4.5c

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (105.7 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 74% yield (56.8 mg, 0.33 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 10 min).

TLC (SiO_2) R_f = 0.25 (heptane: isopropyl acetate =9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 1H), 7.13 (dq, *J* = 6.9, 1.4 Hz, 1H), 6.37 (dd, *J* = 7.0, 5.3 Hz, 1H), 5.91 (ddd, *J* = 17.4, 10.5, 4.9 Hz, 1H), 5.20-5.14 (m, 2H), 4.86 (qdt, *J* = 6.8, 4.9, 1.8 Hz, 1H), 3.46-3.41 (m, 2H), 2.95-2.91 (m, 2H), 1.28 (d, *J* = 6.9Hz, 3H).

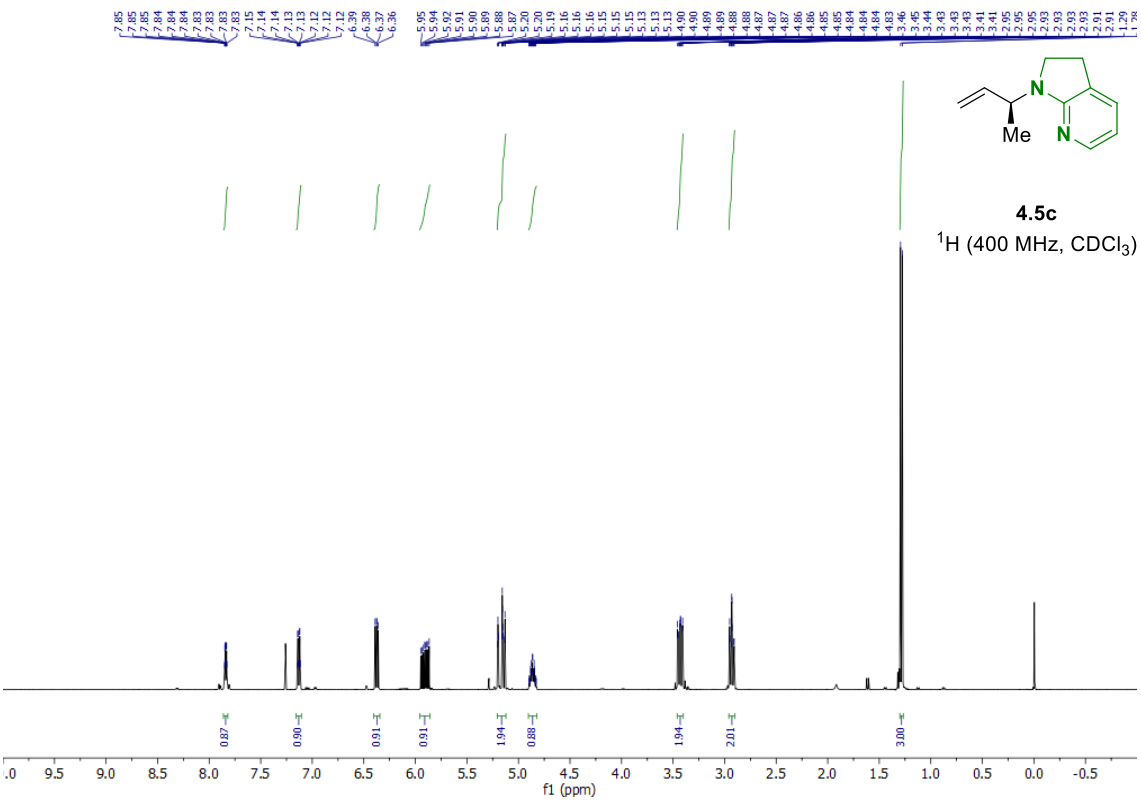
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 145.8, 138.4, 138.4, 130.7, 123.2, 115.4, 111.9, 49.5, 43.6, 25.7, 15.5.

HRMS (ESI): Calculated for $C_{11}H_{14}N_2$ [M+H$^+$] = 175.1230, Found 175.1225.

FTIR (neat): 3709, 2972, 2360, 2341, 1610, 1577, 1491, 1463, 1443, 1391, 771, 669 cm^{-1}.

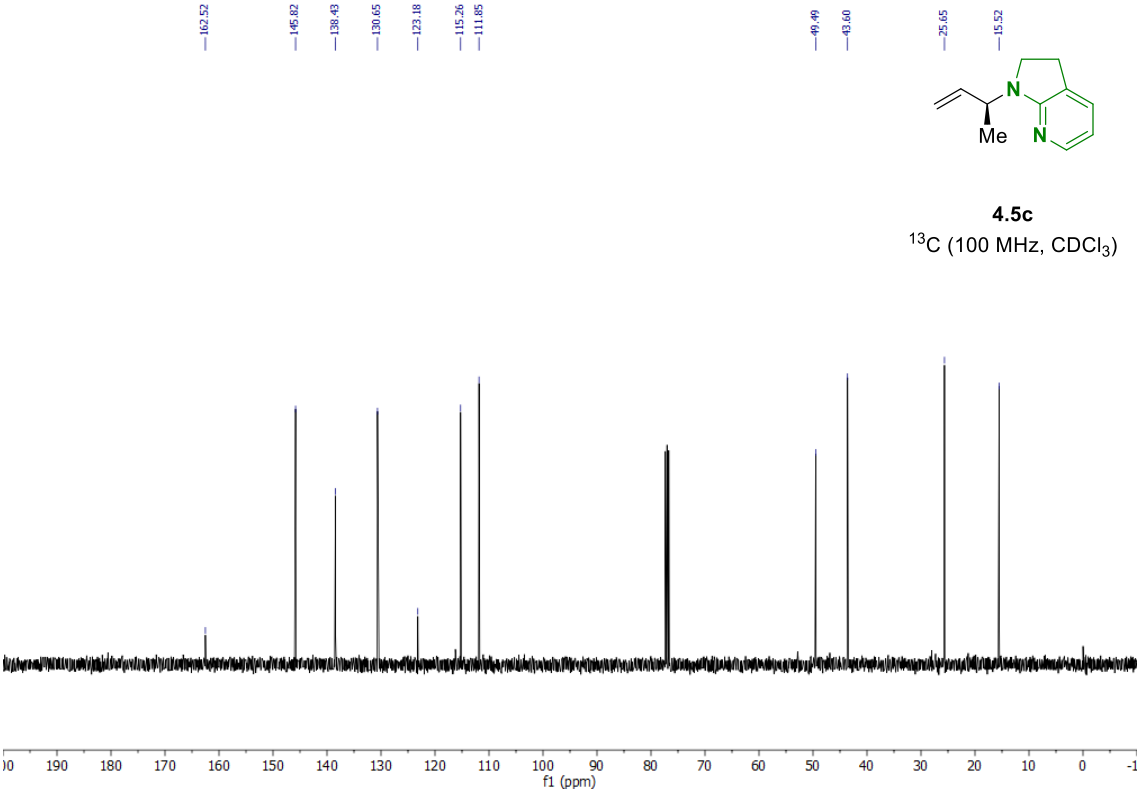
$[\alpha]_D^{28}$= –31.7 (*c* 0.2, $CHCl_3$).

HPLC (Two connected chiralcel OD-3 & OD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 94%.



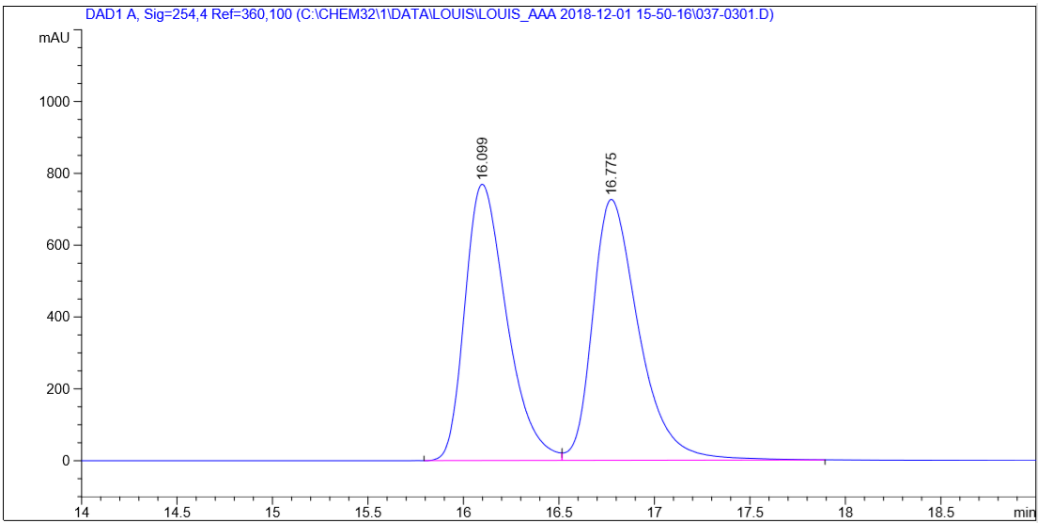
4.5c

^{1}H (400 MHz, $CDCl_3$)

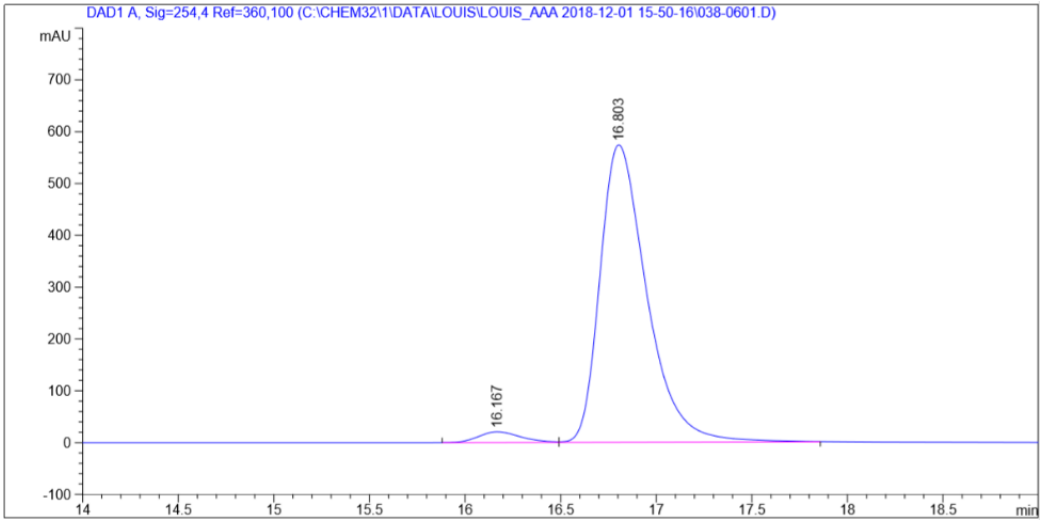


4.5c

^{13}C (100 MHz, $CDCl_3$)

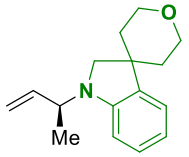


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.099	BV	0.2350	1.16750e4	769.46112	48.9281
2	16.775	VB	0.2557	1.21865e4	726.54614	51.0719



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.167	BV	0.2339	311.74313	20.67129	3.0986
2	16.803	VB	0.2601	9749.09570	574.03931	96.9014

(*S*)-1-(but-3-en-2-yl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (4.5d)



4.5d

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (166.5 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 85% yield (88.9 mg, 0.37 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 10%).

TLC (SiO_2) R_f = 0.33 (heptane: isopropyl acetate =9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11-7.03 (m, 2H), 6.67 (td, *J* = 7.4, 1.0 Hz, 1H), 6.49 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.92 (ddd, *J* = 17.4, 10.5, 5.1 Hz, 1H), 5.22 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.18 (dt, *J* = 3.3, 1.5 Hz, 1H), 4.23 (qdt, *J* = 6.8, 5.1, 1.7 Hz, 1H), 3.97 (ddd, *J* = 11.8, 4.5, 2.2 Hz, 2H), 3.57 (tdd, *J* = 12.0, 7.7, 2.3 Hz, 2H), 3.39-3.29 (m, 2H), 1.97 (dtd, *J* = 13.9, 12.2, 4.7 Hz, 2H), 1.69-1.59 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 3H).

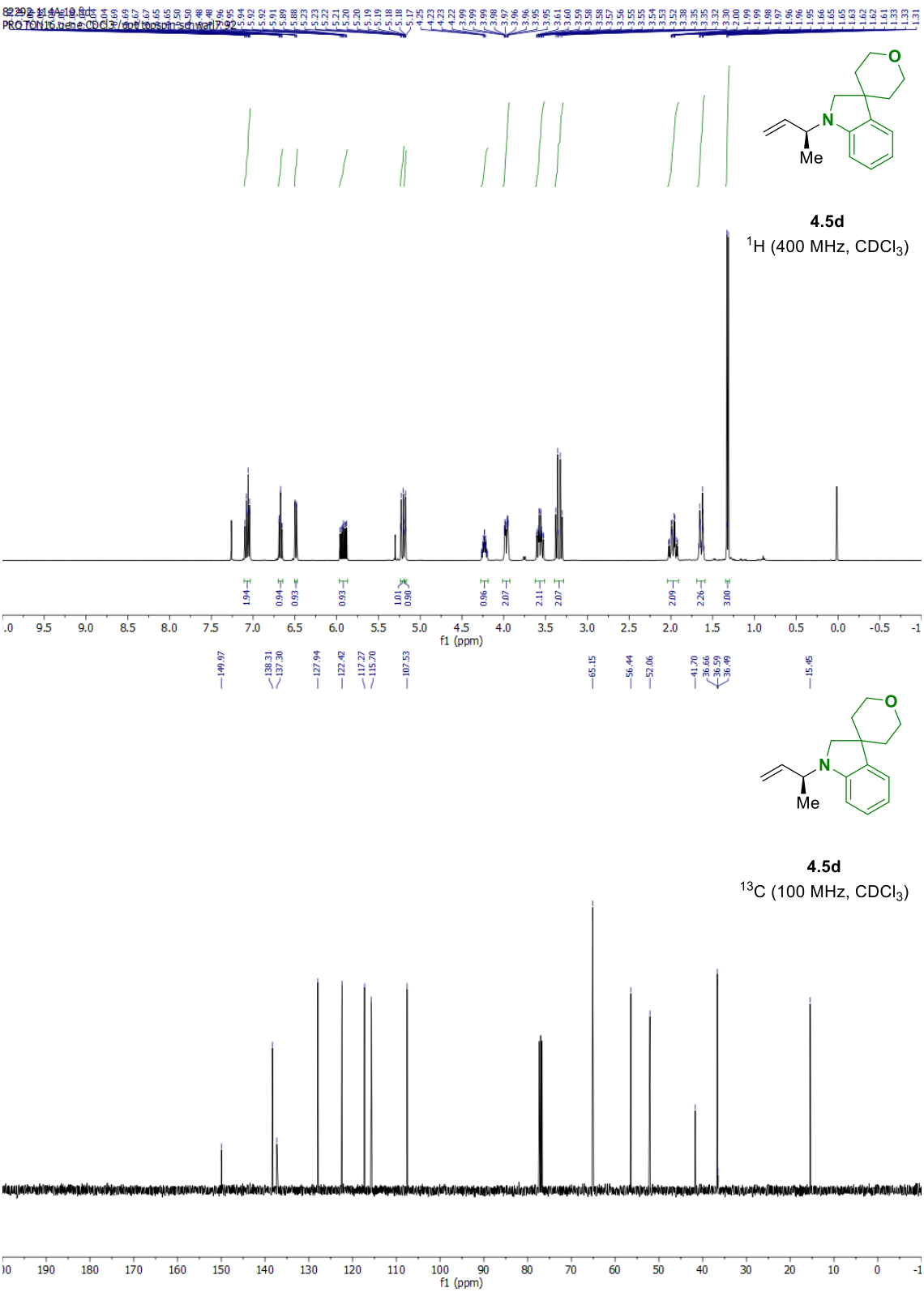
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 138.3, 137.3, 127.9, 122.4, 117.3, 115.7, 107.5, 65.2, 56.4, 52.1, 41.7, 36.7, 36.6, 36.5, 15.5.

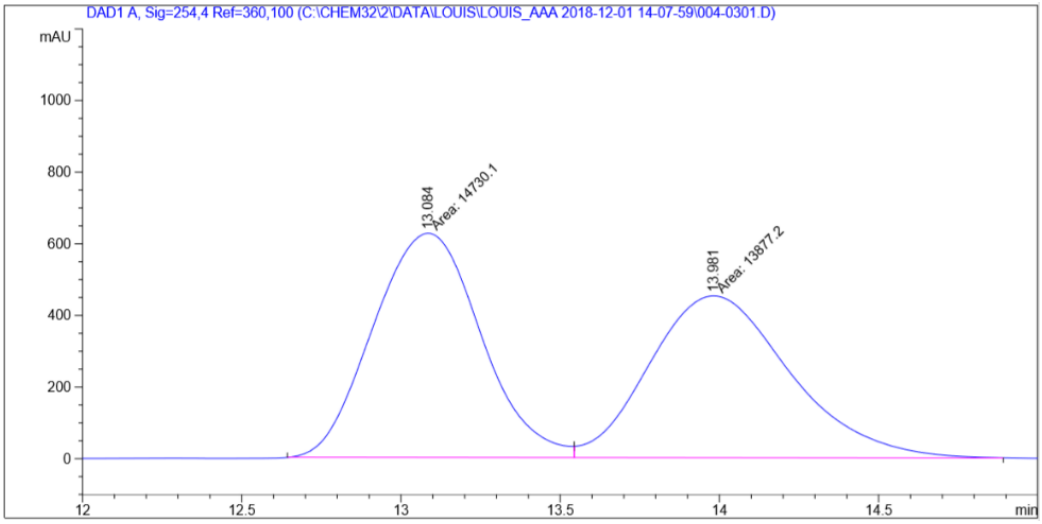
HRMS (ESI): Calculated for $C_{16}H_{22}NO$ $[M+H^+]$ = 244.1696, Found 244.1699.

FTIR (neat): 2936, 2848, 2360, 2341, 1660, 1482, 1462, 1251, 1104, 1027, 837, 750, 668, 547, 464 cm^{-1}.

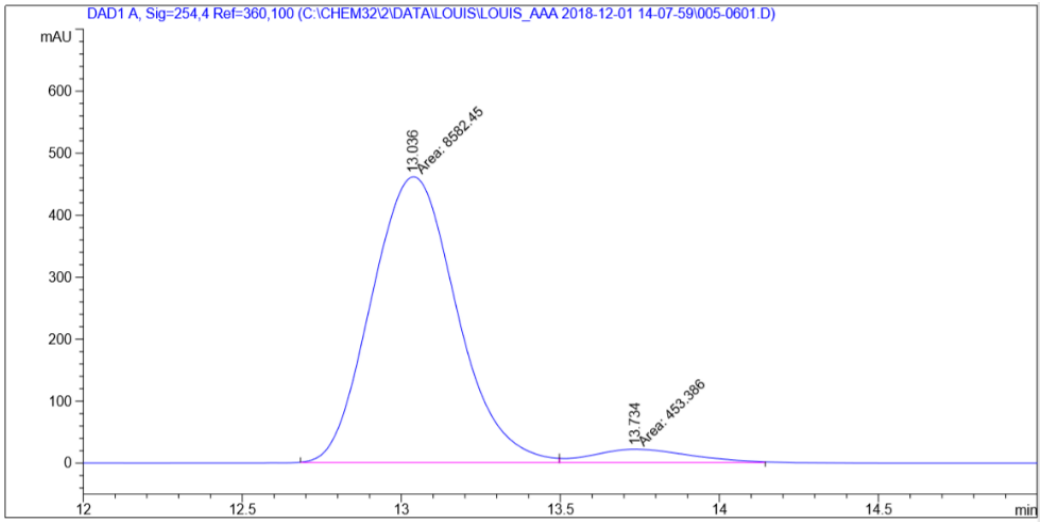
$[\alpha]_D^{28}$ = –44.7 (*c* 0.2, $CHCl_3$).

HPLC (Two connected chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 90%.


O
N
Me
4.5d
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)
O
N
Me
4.5d
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

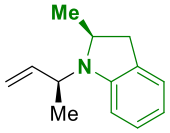


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.084	MF	0.3922	1.47301e4	625.96423	51.4907
2	13.981	FM	0.5117	1.38772e4	451.98029	48.5093



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.036	MF	0.3102	8582.44727	461.11133	94.9824
2	13.734	FM	0.3500	453.38596	21.59124	5.0176

(*S*)-1-((*S*)-but-3-en-2-yl)-2-methylindoline (4.5e)



4.5e

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (117.2 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 80% yield, >20:1 dr (69.2 mg, 0.37 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Heptane).

TLC (SiO_2) R_f = 0.50 (heptane: isopropyl acetate = 9:1).

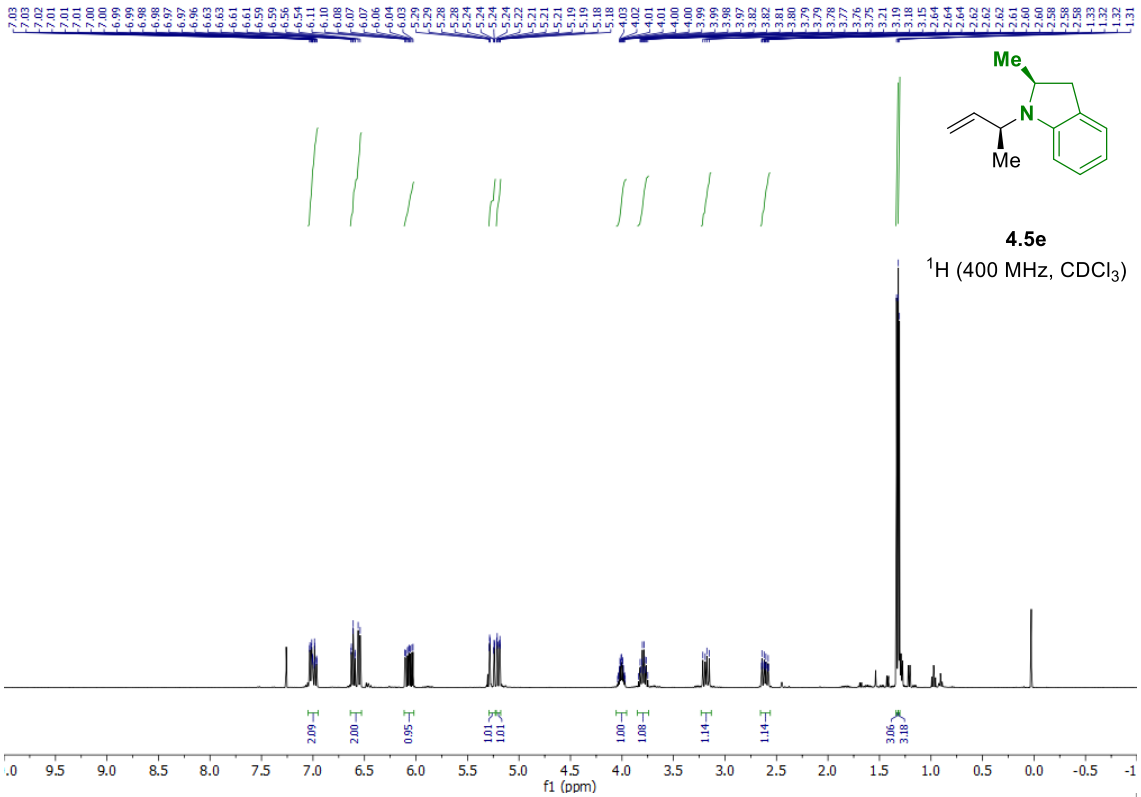
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03-6.96 (m, 2H), 6.63-6.54 (m, 2H), 6.07 (ddd, *J* = 17.5, 10.6, 4.2 Hz, 1H), 5.26 (ddd, *J* = 17.5, 2.1, 1.5 Hz, 1H), 5.20, (ddd, *J* = 10.6, 2.2, 1.5 Hz, 1H), 4.01 (qdt, *J* = 6.8, 4.3, 2.2 Hz, 1H), 3.79 (tq, *J* = 8.9, 6.1 Hz, 1H), 3.18 (dd, *J* = 15.6, 9.1 Hz, 1H), 2.61 (ddt, *J* = 15.7, 8.8, 1.2 Hz, 1H), 1.33 (d, *J* = 5.3 Hz, 3H), 1.31 (d, *J* = 4.4 Hz, 3H).

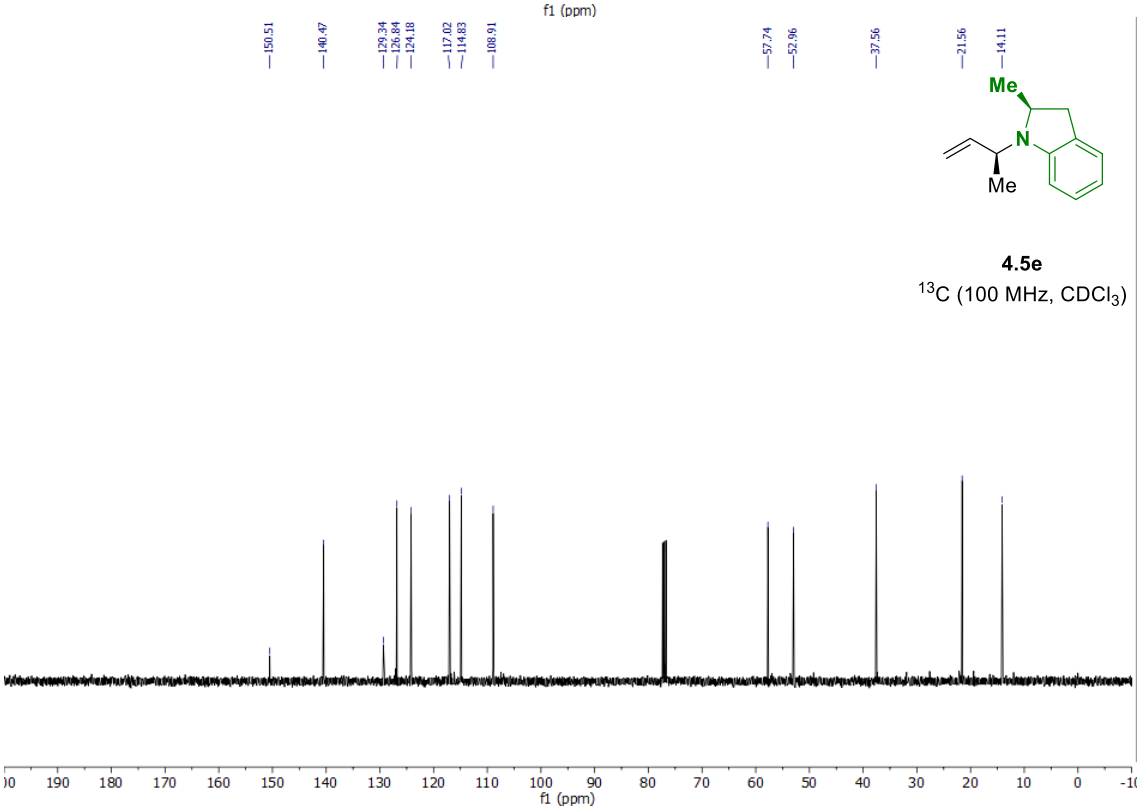
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 140.5, 129.3, 126.8, 124.2, 117.0, 114.8, 108.9, 57.7, 53.0, 37.6, 21.6, 14.1.

HRMS (ESI): Calculated for $C_{13}H_{17}N$ $[M+H^+]$ =188.1434, Found 188.1427.

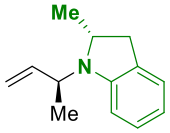
FTIR (neat): 3726, 2966, 2360, 2341, 1605, 1481, 1459, 1257, 772, 747, 720, 669, 656, 419 cm–1.

$[\alpha]_D^{28}$= +57.9 (c 0.2, CHCl3).


Me
N
Me
4.5e
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


Me
N
Me
4.5e
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

(*R*)-1-((*S*)-but-3-en-2-yl)-2-methylindoline (4.5f)



4.5f

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (117.2mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 48% yield, 5:1 dr (39.8 mg, 0.21 mmol) as a light orange oil after purification by flash column chromatography (4g SiO_2, Heptane).

TLC (SiO_2) R_f = 0.50 (heptane: isopropyl acetate = 9:1).

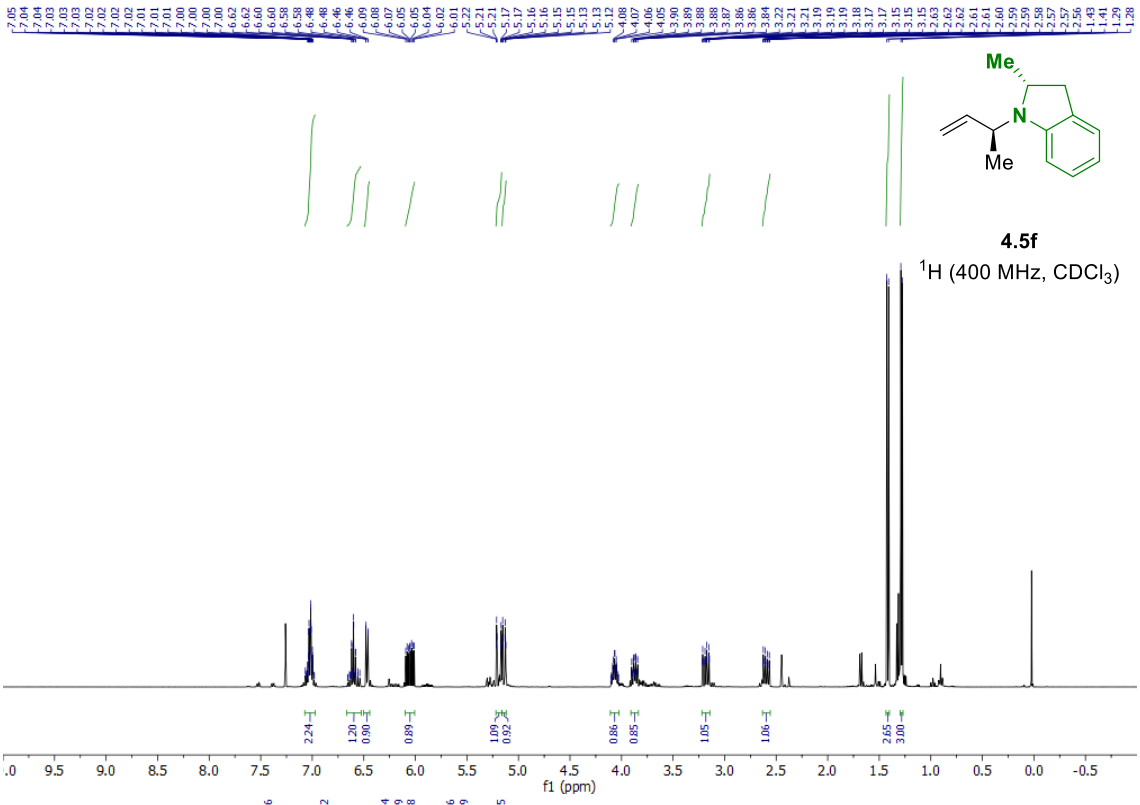
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07-6.98 (m, 2H), 6.66-6.54 (m, 1H), 6.48-6.46 (m, 1H), 6.05 (ddd, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.19 (dt, *J* = 17.4, 1.7 Hz, 1H), 5.14 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.10-4.03 (m, 1H), 3.91-3.84 (m, 1H), 3.18 (ddt, *J* = 15.6, 9.2, 0.9 Hz, 1H), 2.60 (ddt, *J* = 15.6, 7.9, 1.1 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 140.3, 128.9, 127.1, 124.3, 116.8, 114.7, 107.7, 57.0, 53.4, 37.6, 22.0, 16.4.

HRMS (ESI): Calculated for $C_{13}H_{17}N$ $[M+H^+]$ =188.1434, Found 188.1428.

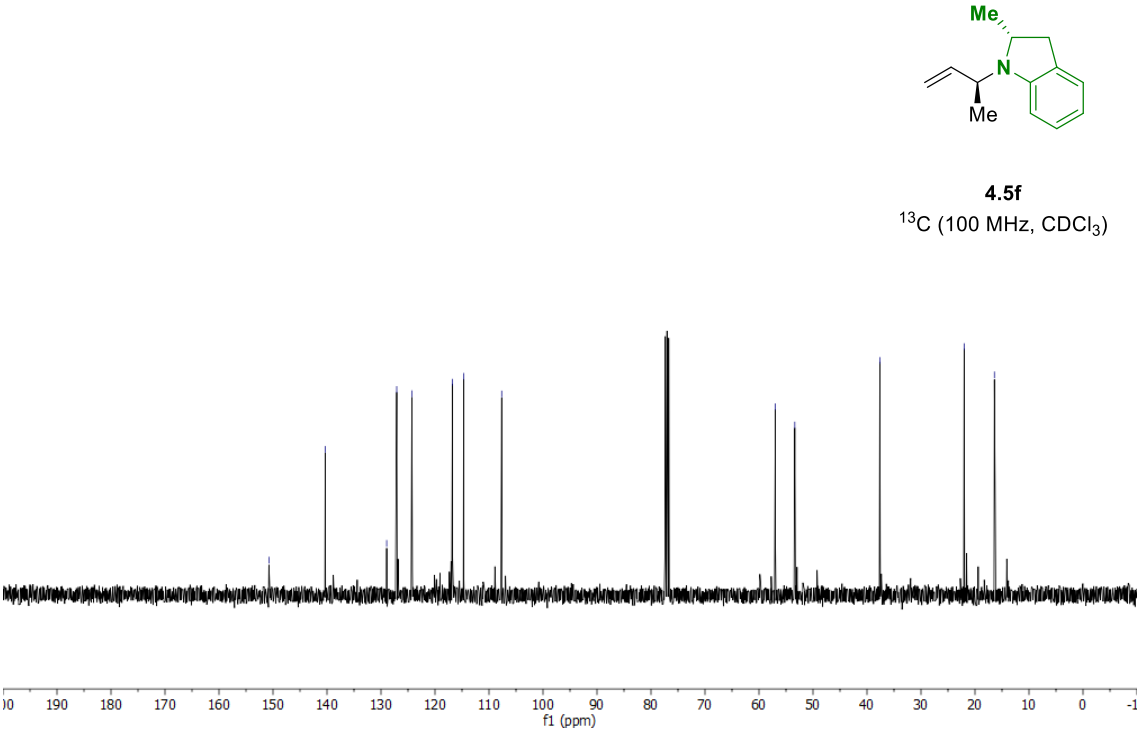
FTIR (neat): 3706, 3627, 2971, 2360, 2341, 1606, 1483, 1459, 1258, 746, 720, 669, 409 cm^{-1}.

$[\alpha]_D^{28}$= –24.6 (*c* 0.2, $CHCl_3$).



4.5f

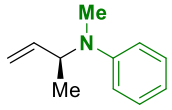
^{1}H (400 MHz, $CDCl_3$)



4.5f

^{13}C (100 MHz, $CDCl_3$)

(*S*)-*N*-(but-3-en-2-yl)-*N*-methylaniline (4.5g)



4.5g

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (94.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 71% yield (50.3 mg, 0.31 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Heptane).

TLC (SiO_2) R_f = 0.47 (heptane: isopropyl acetate = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.19 (m, 2H), 6.82-6.77 (m, 2H), 6.70 (tt, *J* = 7.3, 1.0 Hz, 1H), 5.91 (ddd, *J* = 17.2, 10.8, 4.2 Hz, 1H), 5.17 (p, *J* = 1.4 Hz, 1H), 5.13 (ddd, *J* = 9.3, 2.0, 1.4 Hz, 1H), 4.48 (qdt, *J* = 6.6, 4.1, 2.0 Hz, 1H), 2.73 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H).

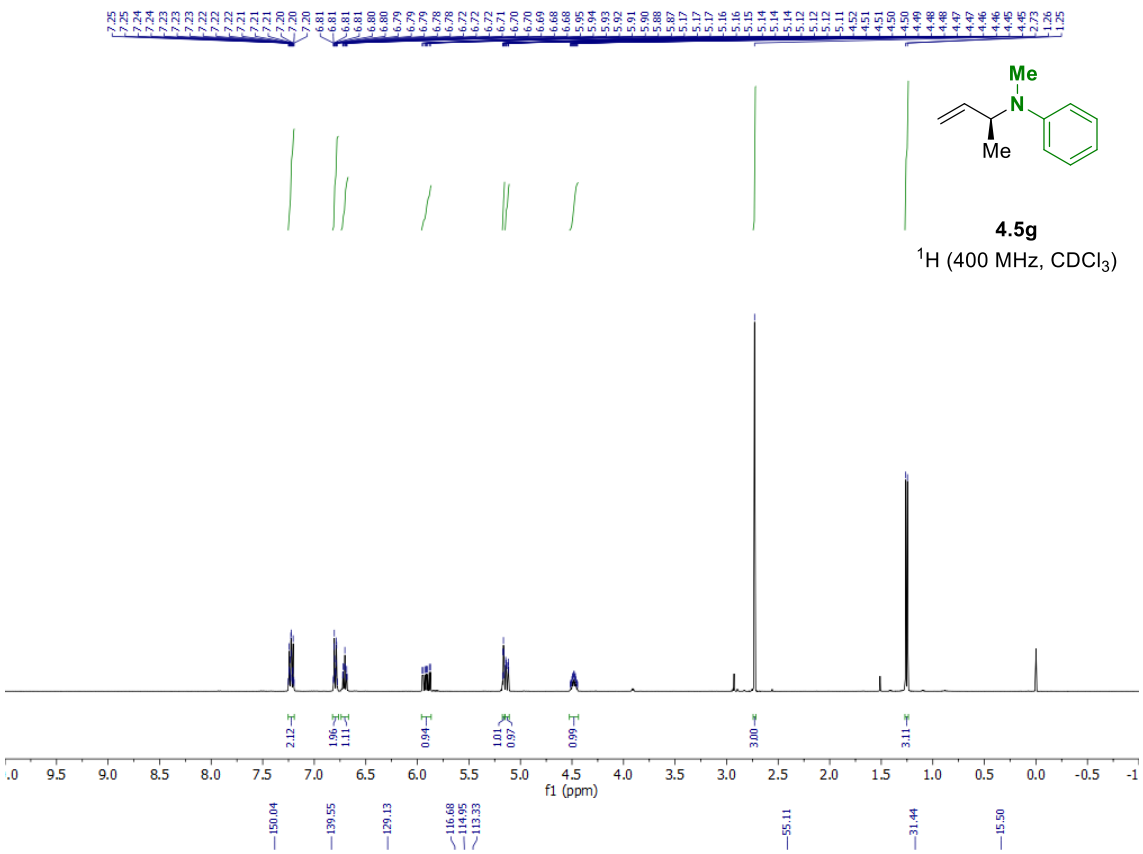
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 139.6, 129.1, 116.7, 115.0, 133.3, 55.1, 31.4, 15.5.

HRMS (ESI): Calculated for $C_{11}H_{15}N$ [M+H$^+$] = 162.1277, Found 162.1278.

FTIR (neat): 3061, 2973, 2812, 2360, 2341, 1597, 1501, 1308, 1137, 1035, 990, 917, 746, 690, 518cm^{-1}.

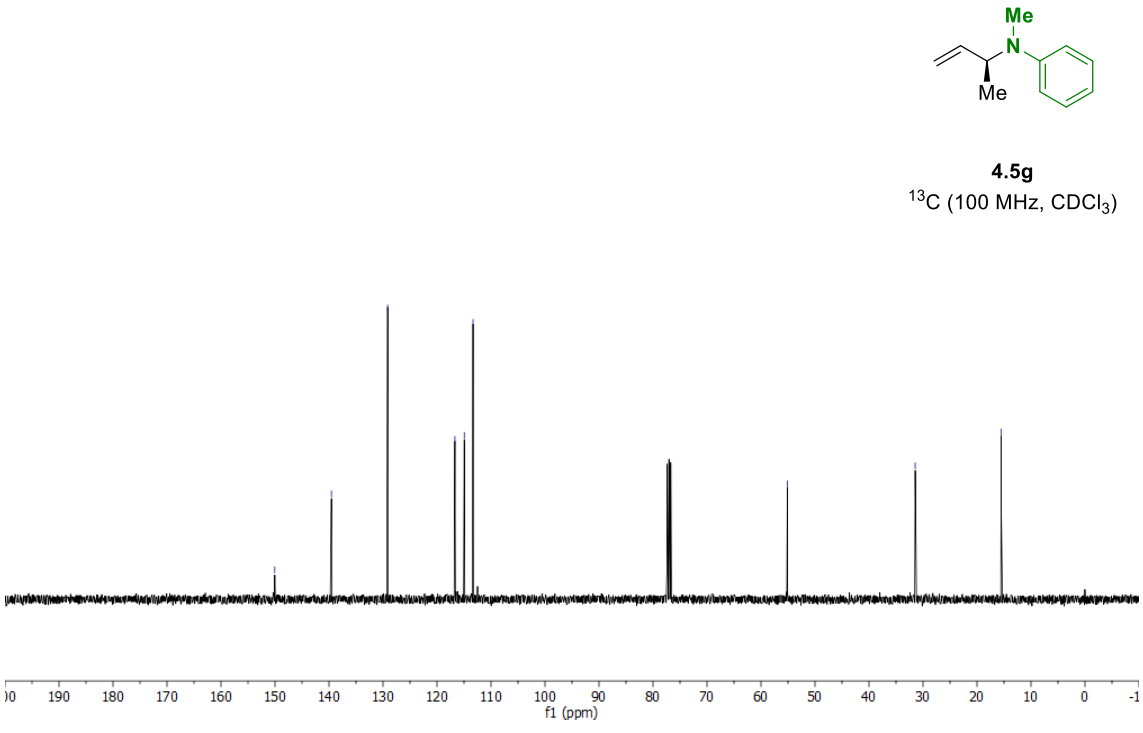
$[\alpha]_D^{28}$= –185.6 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 91%.



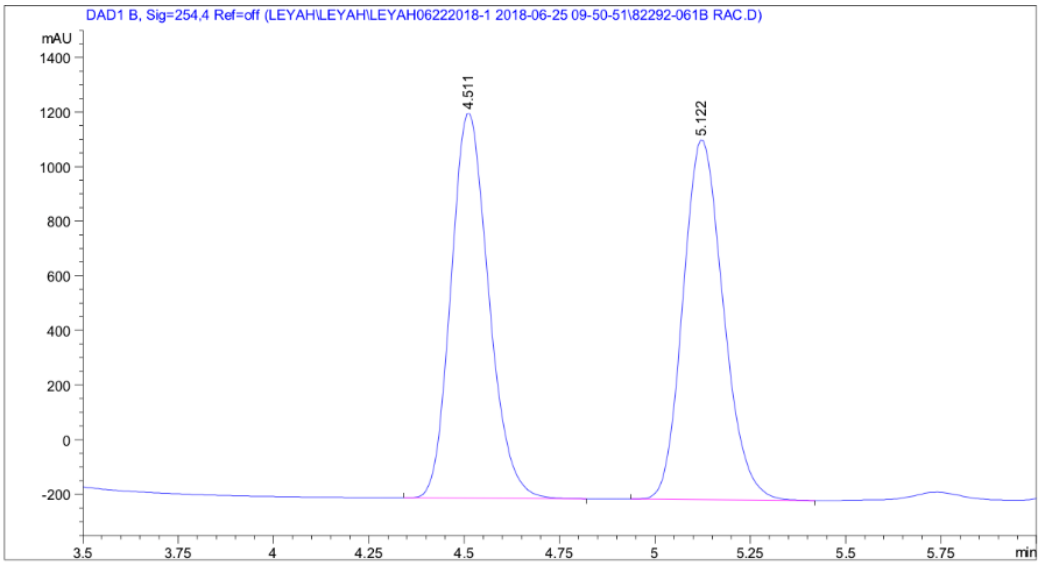
4.5g

^{1}H (400 MHz, $CDCl_3$)

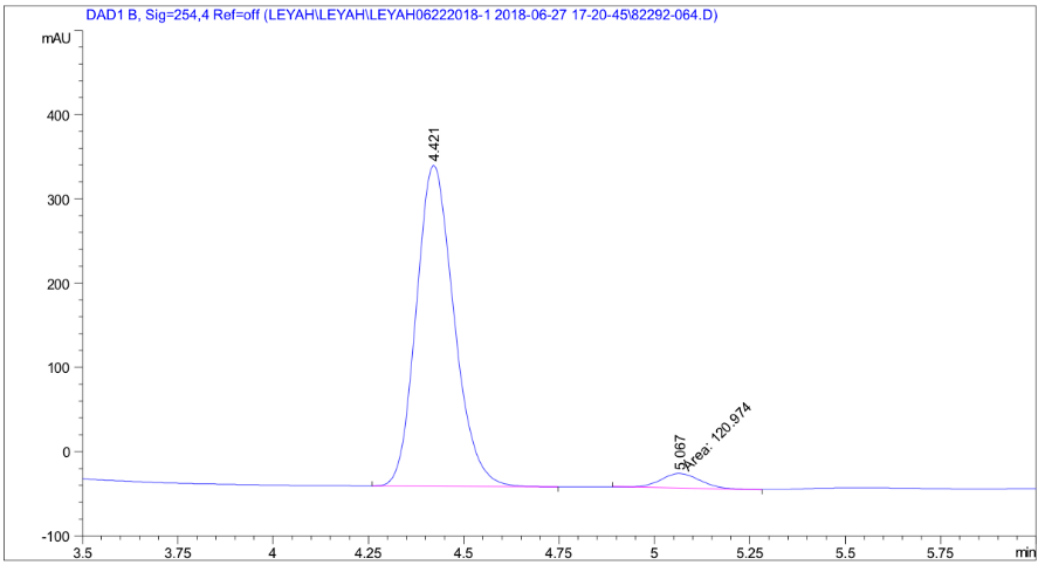


4.5g

^{13}C (100 MHz, $CDCl_3$)

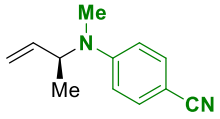


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.511	BB	0.1061	9688.04102	1411.46924	50.0019
2	5.122	BB	0.1137	9687.29688	1318.63684	49.9981



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.421	BB	0.1062	2622.18921	381.43484	95.5900
2	5.067	MM	0.1176	120.97383	17.14165	4.4100

(*S*)-4-(but-3-en-2-yl(methyl)amino)benzonitrile (4.5h)



4.5h

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (116.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 79% yield (64.7 mg, 0.35 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 10 min).

TLC (SiO_2) R_f = 0.25 (heptane: isopropyl acetate = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.43 (m, 2H), 6.74-6.69 (m, 2H), 5.86 (ddd, *J* = 17.3, 10.6, 4.0 Hz, 1H), 5.21 (ddd, *J* = 10.6, 2.0, 1.1 Hz, 1H), 5.14 (ddd, *J* = 17.4, 2.0, 1.1, 1H), 4.53 (qdt, *J* = 6.7, 4.1, 2.0 Hz, 1H), 2.81 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H).

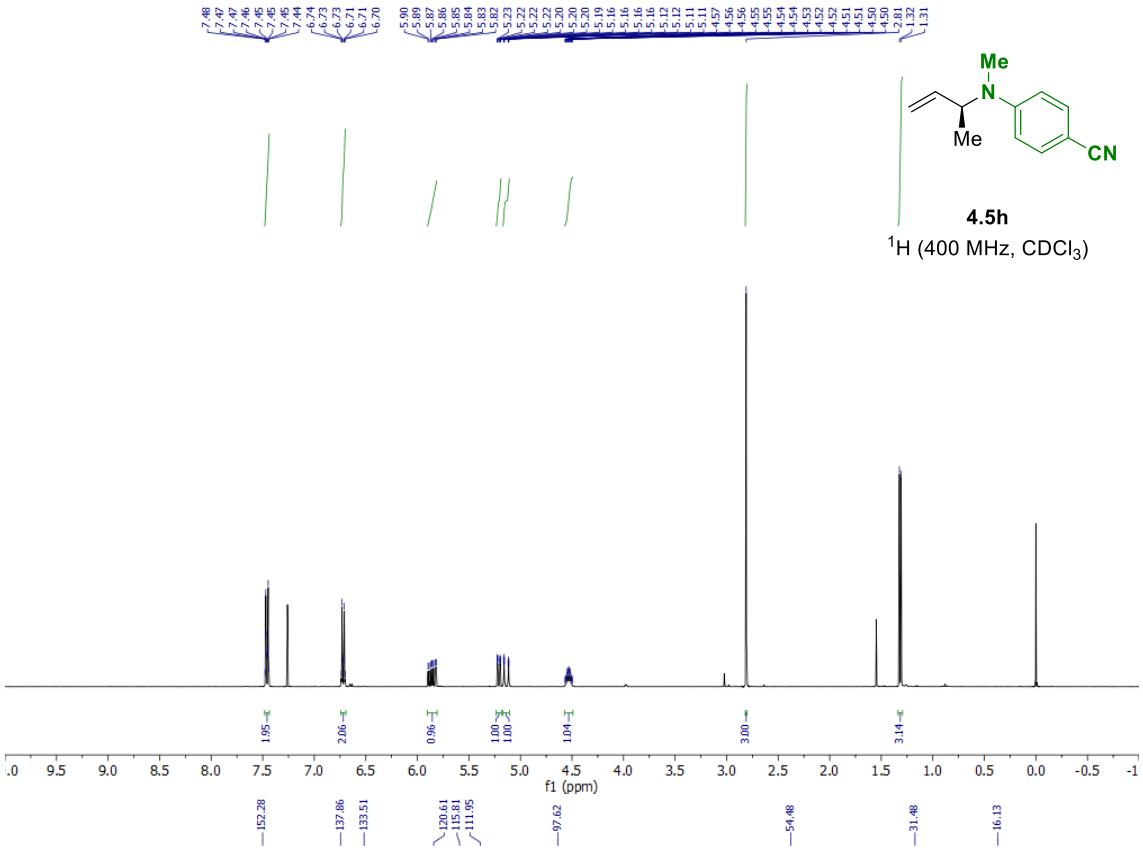
^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 137.9, 133.5, 120.6, 115.8, 112.0, 97.6, 54.5, 31.5, 16.1.

HRMS (ESI): Calculated for $C_{12}H_{14}N_2$ [M+H$^+$] = 187.1230, Found 187.1231.

FTIR (neat): 3726, 3627, 2360, 2341, 2111, 1602, 1517, 1383, 1179, 1111, 922, 816, 669, 543 cm^{-1}.

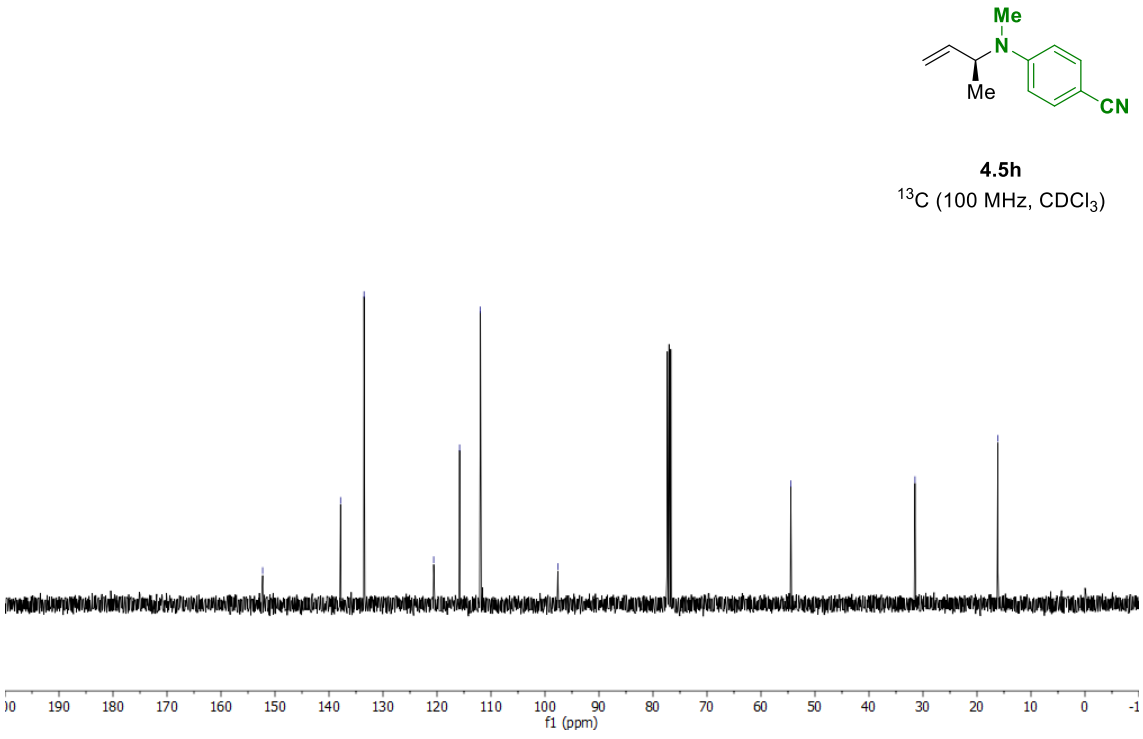
$[\alpha]_D^{28}$= –207.8 (*c* 0.2, $CHCl_3$).

HPLC (Two connected chiralcel OD-3 & OD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 90%.



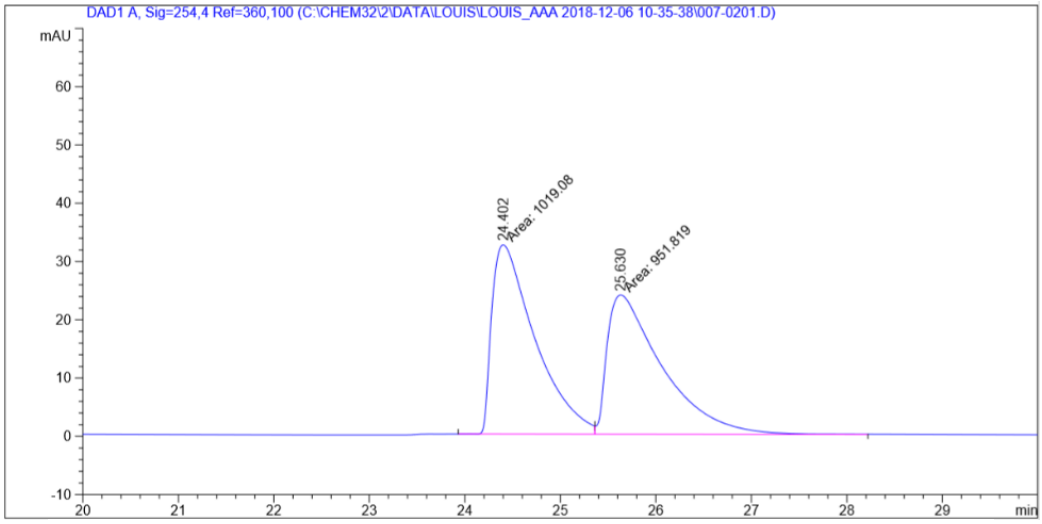
4.5h

^{1}H (400 MHz, $CDCl_3$)

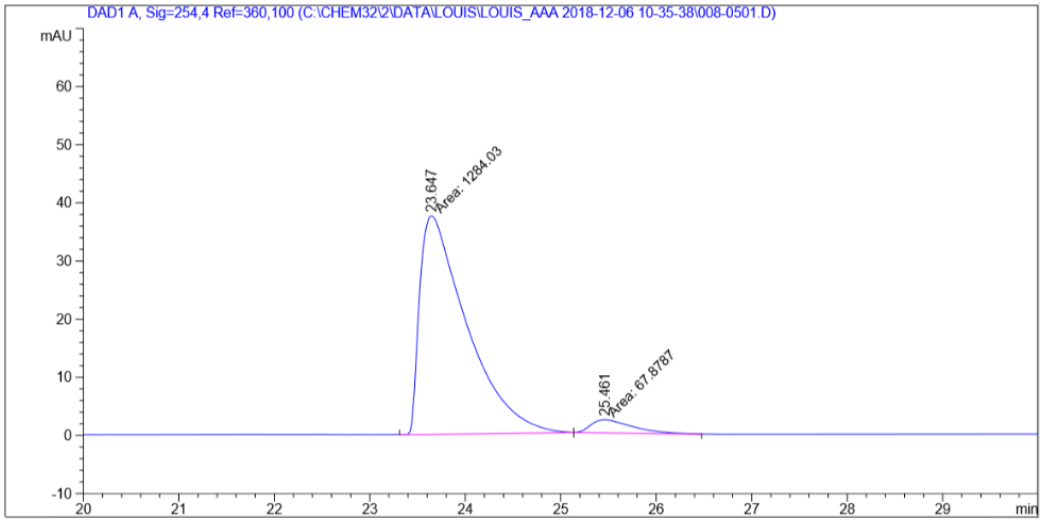


4.5h

^{13}C (100 MHz, $CDCl_3$)

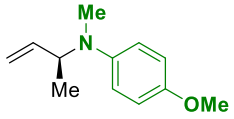


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.402	MF	0.5228	1019.07697	32.49002	51.7063
2	25.630	FM	0.6645	951.81891	23.87190	48.2937



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.647	MM	0.5696	1284.03052	37.56815	94.9790
2	25.461	MM	0.5000	67.87875	2.26275	5.0210

(*S*)-N-(but-3-en-2-yl)-4-methoxy-N-methylaniline (4.5i)



4.5i

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the secondary amine (120.7 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 89% yield (74.9 mg, 0.39 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 25:1–10:1).

TLC (SiO_2) R_f = 0.38 (hexanes: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 – 6.77 (m, 4H), 5.92 (ddd, *J* = 17.2, 10.7, 4.6 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.28 (dtdd, *J* = 8.5, 6.6, 3.9, 1.8 Hz, 1H), 3.77 (s, 3H), 2.67 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H).

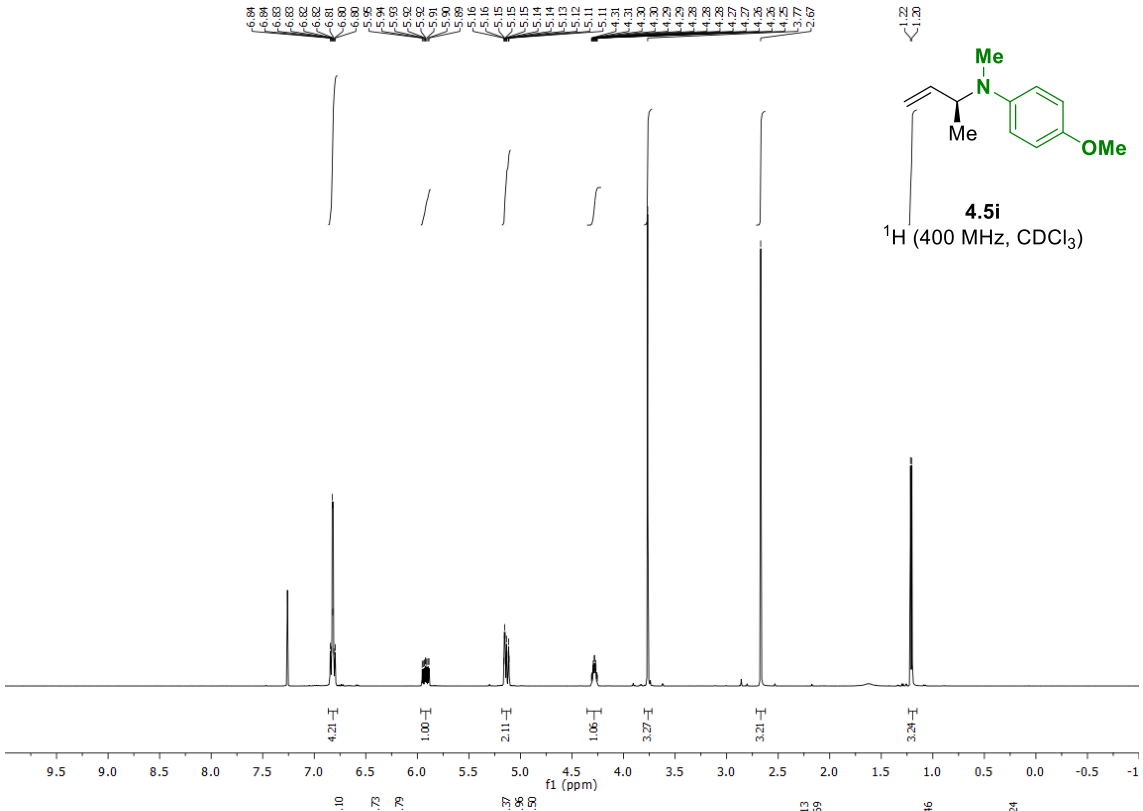
^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 144.7, 139.8, 116.4, 115.0, 114.5, 57.1, 55.7, 32.5, 15.2.

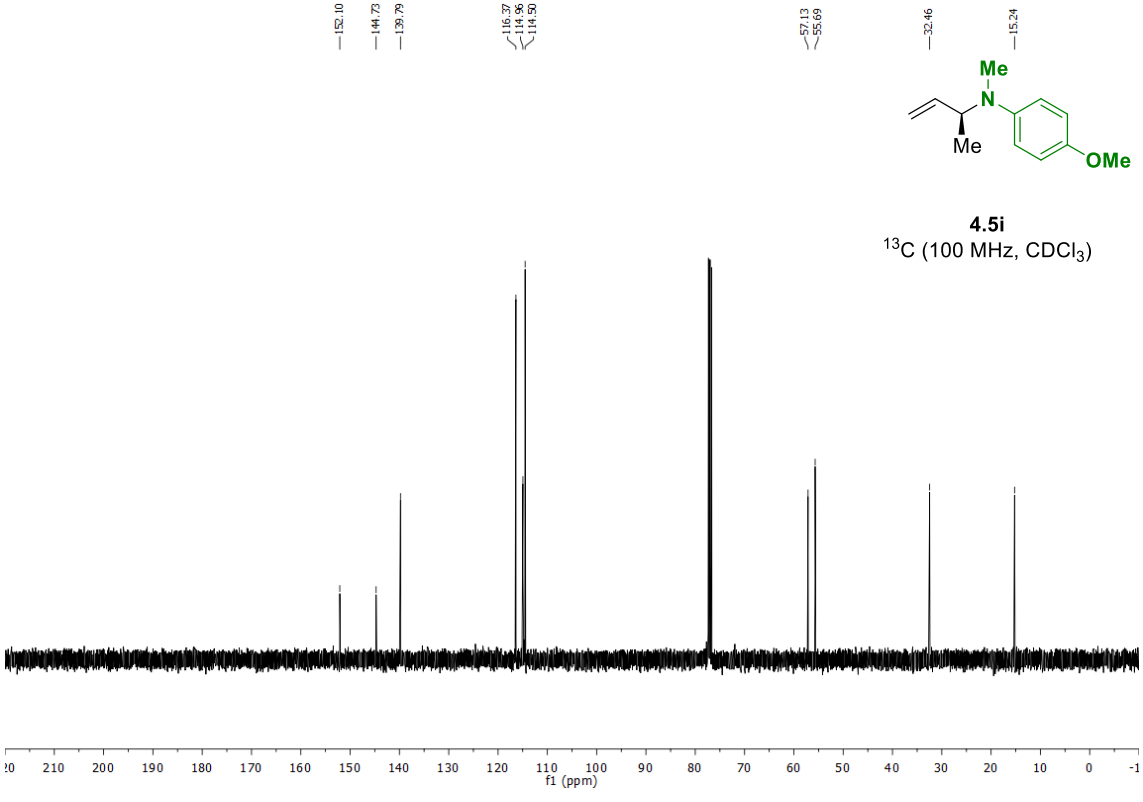
HRMS (ESI): Calculated for $C_{12}H_{17}NO$ $[M+H^+]$ = 192.1383, Found 192.1381.

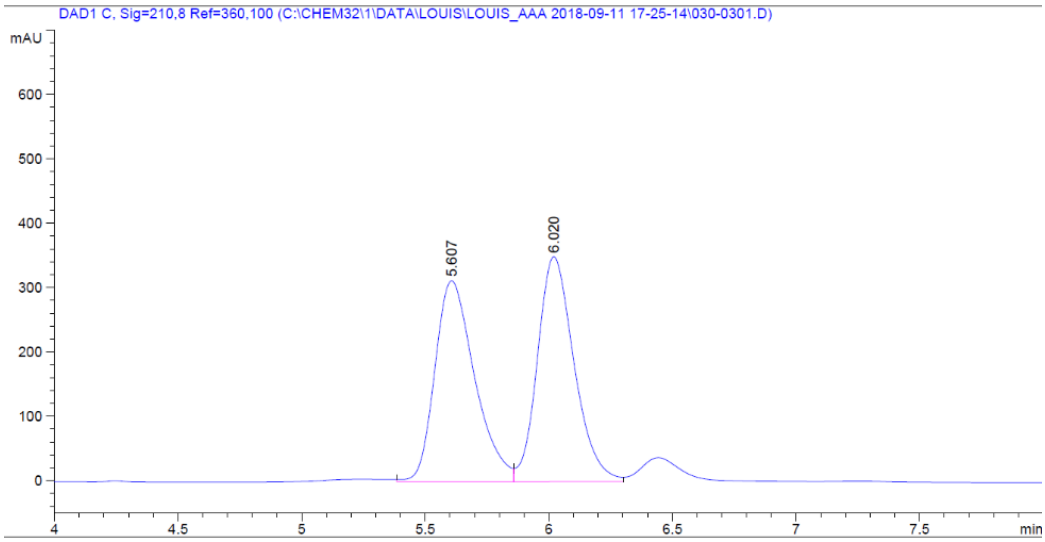
FTIR (neat): 2975, 1509, 1464, 1242, 1110, 1039, 919, 815, 754 cm^{-1}.

$[\alpha]_D^{28}$= –112.0 (*c* 1.0, $CHCl_3$).

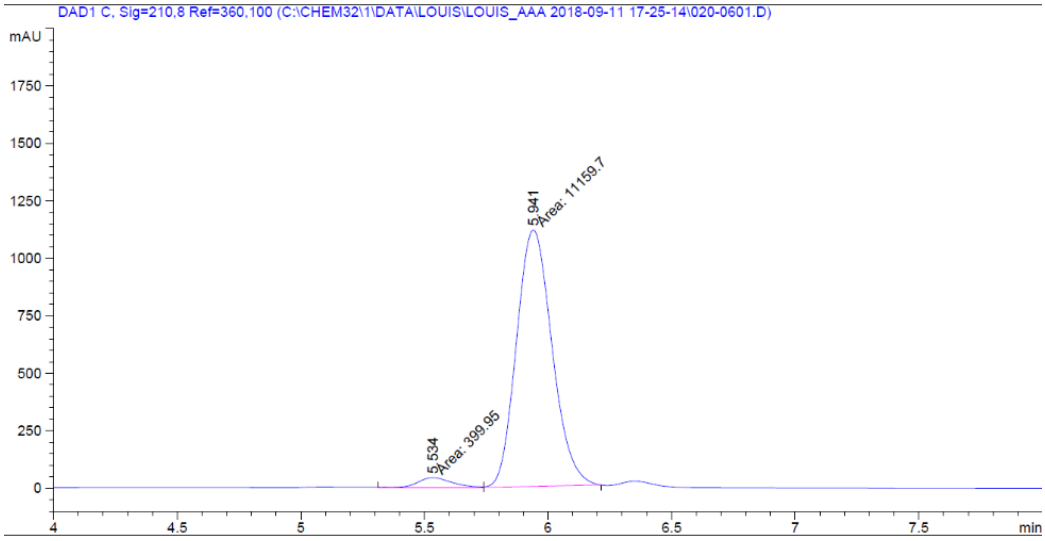
HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 210 nm), *ee* = 93%.


Me
N
Me
OMe
4.5i
1H (400 MHz, CDCl3)
f1 (ppm)


Me
N
Me
OMe
4.5i
13C (100 MHz, CDCl3)
f1 (ppm)

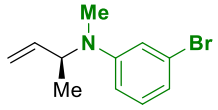


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.607	VV	0.1706	3501.72437	312.76028	49.2364
2	6.020	VV	0.1584	3610.33838	349.97104	50.7636



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.534	MM	0.1567	399.95032	42.53660	3.4599
2	5.941	MM	0.1665	1.11597e4	1116.88684	96.5401

(*S*)-3-bromo-N-(but-3-en-2-yl)-N-methylaniline (4.5j)



4.5j

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the secondary amine (163.7 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 60 hr). The title compound was obtained in 64% yield (67.6 mg, 0.28 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 40:1–20:1).

TLC (SiO_2) R_f = 0.59 (hexanes: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06 (t, *J* = 8.1 Hz, 1H), 6.89 (t, *J* = 2.2 Hz, 1H), 6.81 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (ddd, *J* = 17.4, 10.6, 4.1 Hz, 1H), 5.20 – 5.11 (m, 2H), 4.44 (qdt, *J* = 6.5, 4.0, 2.0 Hz, 1H), 2.72 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H).

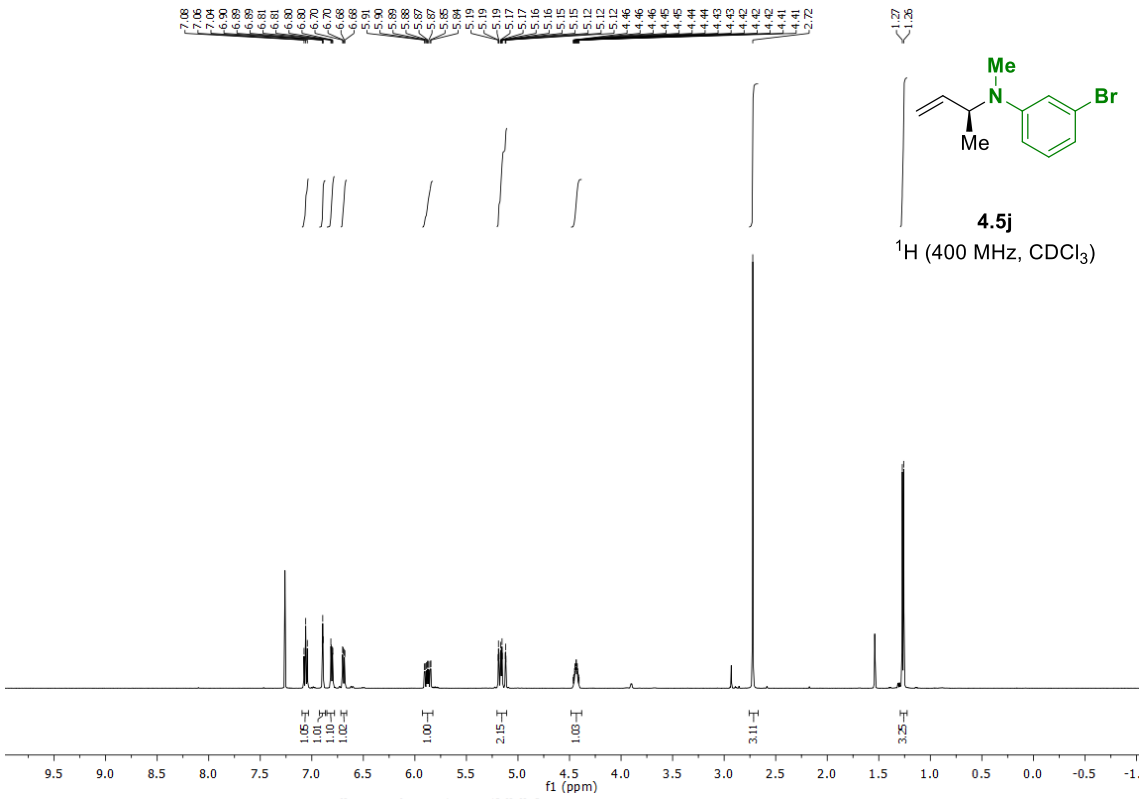
^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 138.8, 130.2, 123.4, 119.2, 115.7, 115.3, 111.5, 54.9, 31.4, 15.7.

HRMS (ESI): Calculated for $C_{11}H_{14}BrN$ [M+H$^+$] = 240.0382, Found 240.0382.

FTIR (neat): 1590, 1554, 1487, 1215, 1114, 981, 925, 752, 681 cm^{-1}.

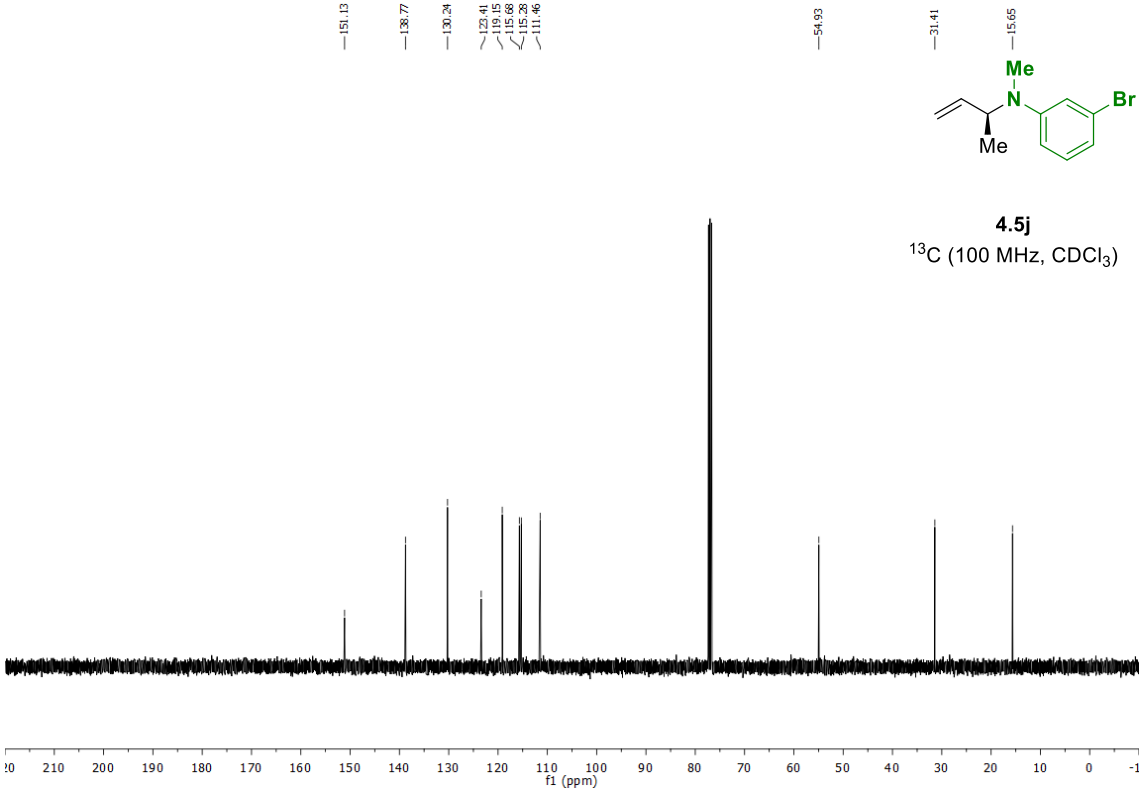
$[\alpha]_D^{28}$= –95.8 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel OD-3 column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 90%.



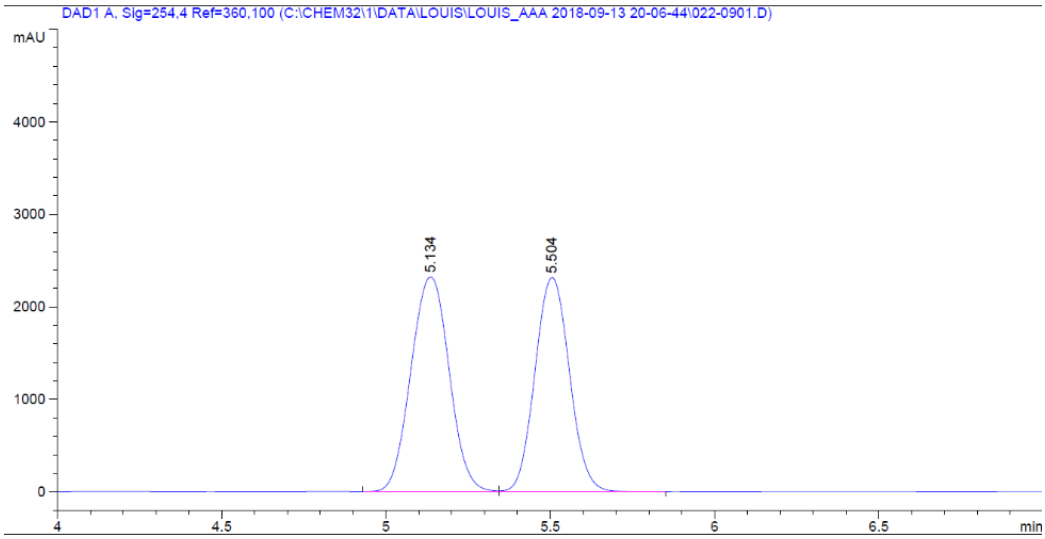
4.5j

^{1}H (400 MHz, $CDCl_3$)

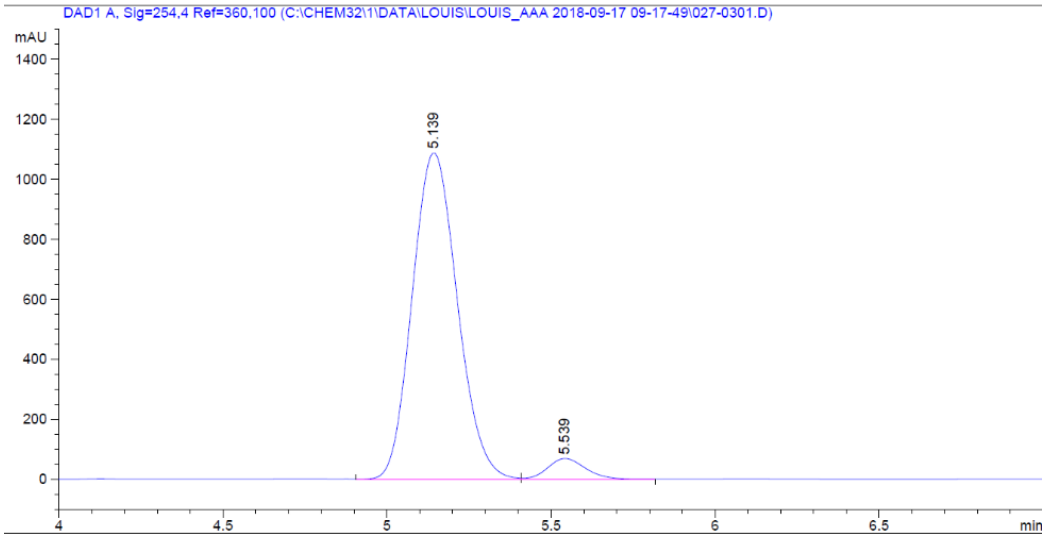


4.5j

^{13}C (100 MHz, $CDCl_3$)

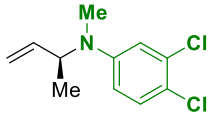


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.134	VV	0.1282	1.87770e4	2325.36768	52.6472
2	5.504	VB	0.1150	1.68887e4	2317.19702	47.3528



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.139	VV	0.1494	1.03940e4	1088.91272	94.9763
2	5.539	VB	0.1230	549.78442	68.94199	5.0237

(*S*)-N-(but-3-en-2-yl)-3,4-dichloro-N-methylaniline (4.5k)



4.5k

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the secondary amine (154.9 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 60 hr). The title compound was obtained in 76% yield (76.9 mg, 0.33 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 40:1–20:1).

TLC (SiO_2) R_f = 0.59 (hexanes: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 1H), 6.81 (d, *J* = 2.9 Hz, 1H), 6.60 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.86 (ddd, *J* = 17.4, 10.6, 4.1 Hz, 1H), 5.18 (ddd, *J* = 10.6, 2.0, 1.2 Hz, 1H), 5.13 (ddd, *J* = 17.4, 2.0, 1.2 Hz, 1H), 4.39 (qdt, *J* = 6.5, 4.1, 2.1 Hz, 1H), 2.71 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 3H).

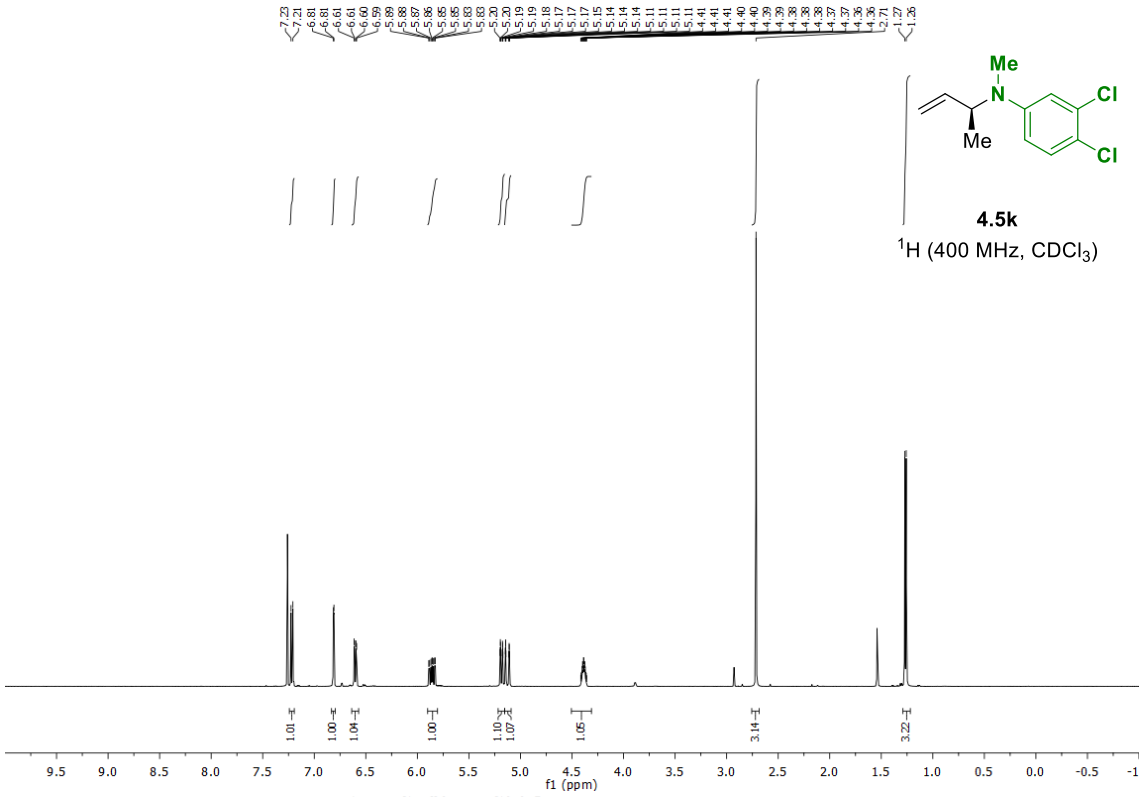
^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 138.4, 132.7, 130.3, 118.9, 115.5, 114.3, 112.5, 55.2, 31.5, 15.7.

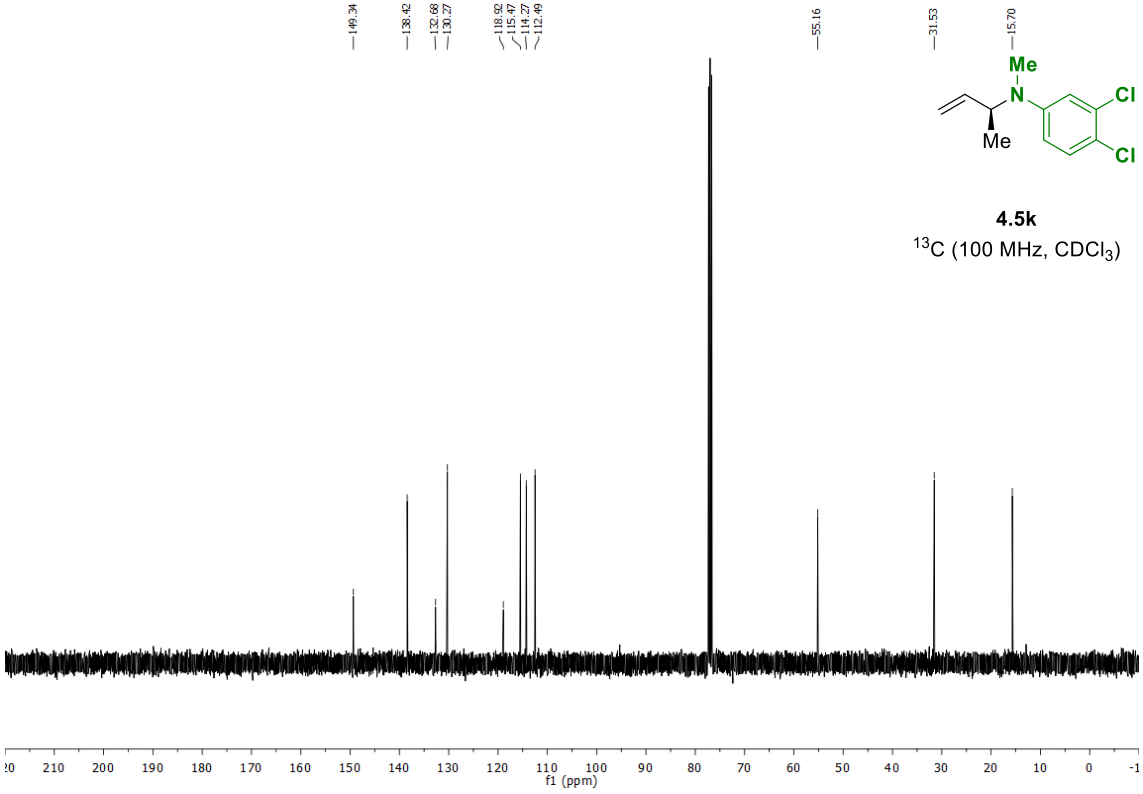
HRMS (ESI): Calculated for $C_{11}H_{13}Cl_2N$ [M+H$^+$] = 230.0498, Found 230.0496.

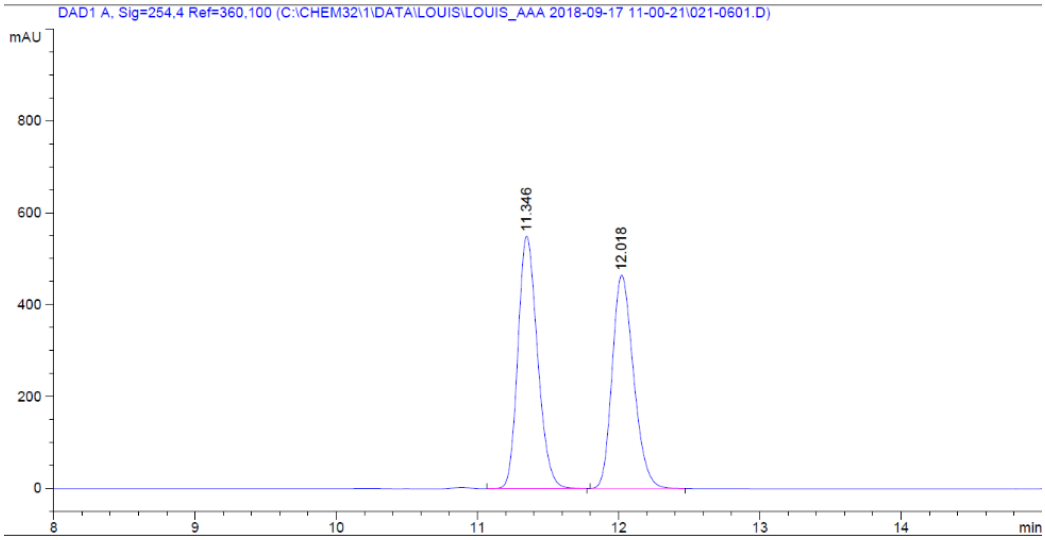
FTIR (neat): 2976, 1593, 1487, 1371, 1214, 1112, 997, 924 cm^{-1}.

$[\alpha]_D^{28}$= –100.0 (*c* 1.0, $CHCl_3$).

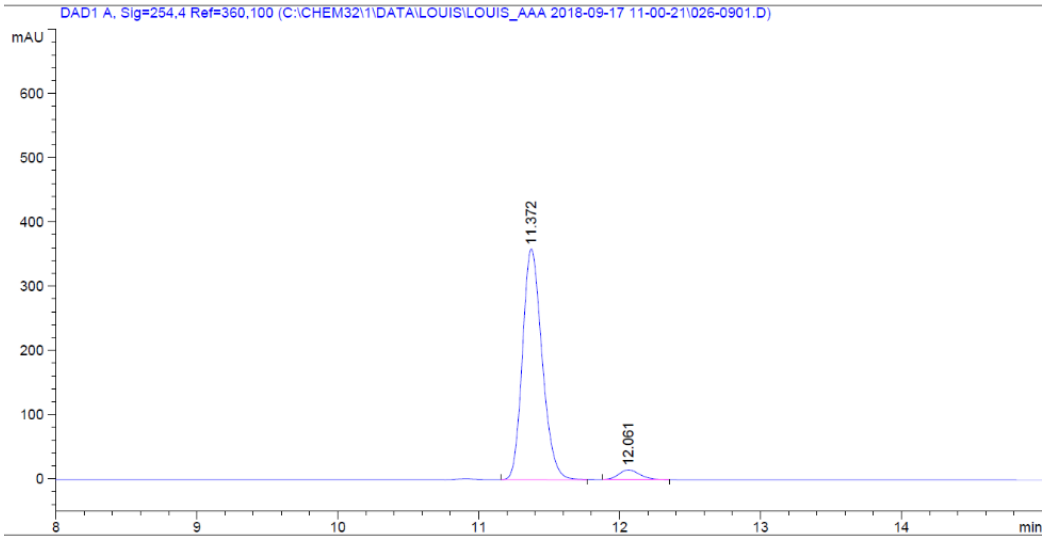
HPLC (Two connected chiralcel OD-3 & OD-H column, hexanes:*i*-PrOH = 99.5:0.5, 1.00 mL/min, 254 nm), *ee* = 91%.


Me
N
Me
Cl
Cl
4.5k
1H (400 MHz, CDCl3)
f1 (ppm)


Me
N
Me
Cl
Cl
4.5k
13C (100 MHz, CDCl3)
f1 (ppm)

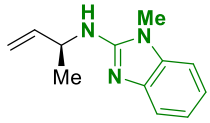


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.346	VB	0.1486	5312.18115	550.45233	52.0154
2	12.018	BB	0.1629	4900.53076	465.21292	47.9846



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.372	BB	0.1507	3472.61035	359.44650	95.5948
2	12.061	BB	0.1602	160.02368	15.27661	4.4052

(*S*)-*N*-(but-3-en-2-yl)-*N*,1-dimethyl-1*H*-benzo[*d*]imidazole-2-amine (4.5l)



4.5l

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the primary amine (141.9 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 ^{o}C, 24 hr). The title compound was obtained in 94% yield (89.1 mg, 0.41 mmol) as a light orange oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 20%).

TLC (SiO_2) R_f = 0.25 (heptane: isopropyl acetate = 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61-7.58 (m, 1H), 7.20-7.14 (m, 4H), 6.02 (ddd, *J* = 17.4, 10.5, 4.9 Hz, 1H), 5.29-5.25 (m, 1H), 5.25-5.23 (m, 1H), 4.16 (qdt, *J* = 6.8, 4.9, 1.8 Hz, 1H), 3.61 (d, 3H), 2.84 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H).

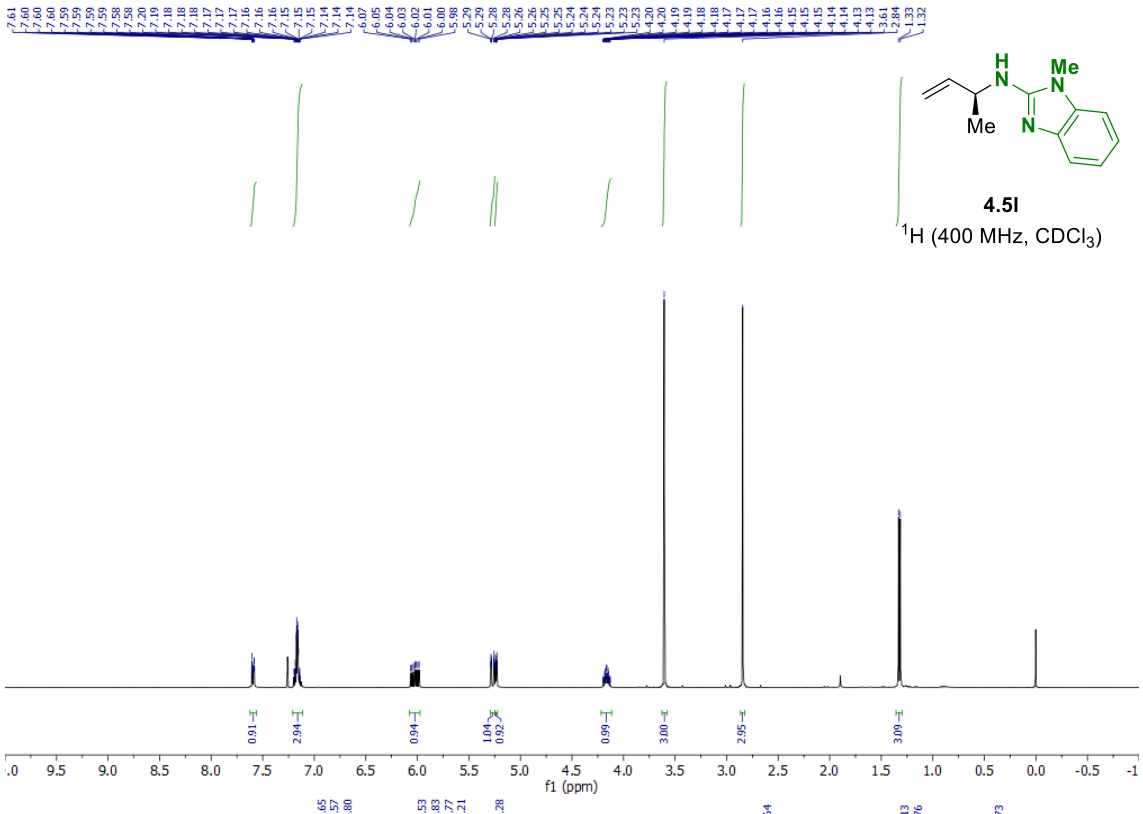
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 138.6, 135.8, 121.5, 120.8, 117.8, 116.2, 108.3, 58.6, 33.1, 30.8, 15.7.

HRMS (ESI): Calculated for $C_{13}H_{17}N_3$ [M+H$^+$] = 216.1495, Found 216.1498.

FTIR (neat): 2972, 2360, 2341, 1615, 1594, 1524, 1463, 1390, 1285, 1116, 922, 800, 741, 669 cm^{-1}.

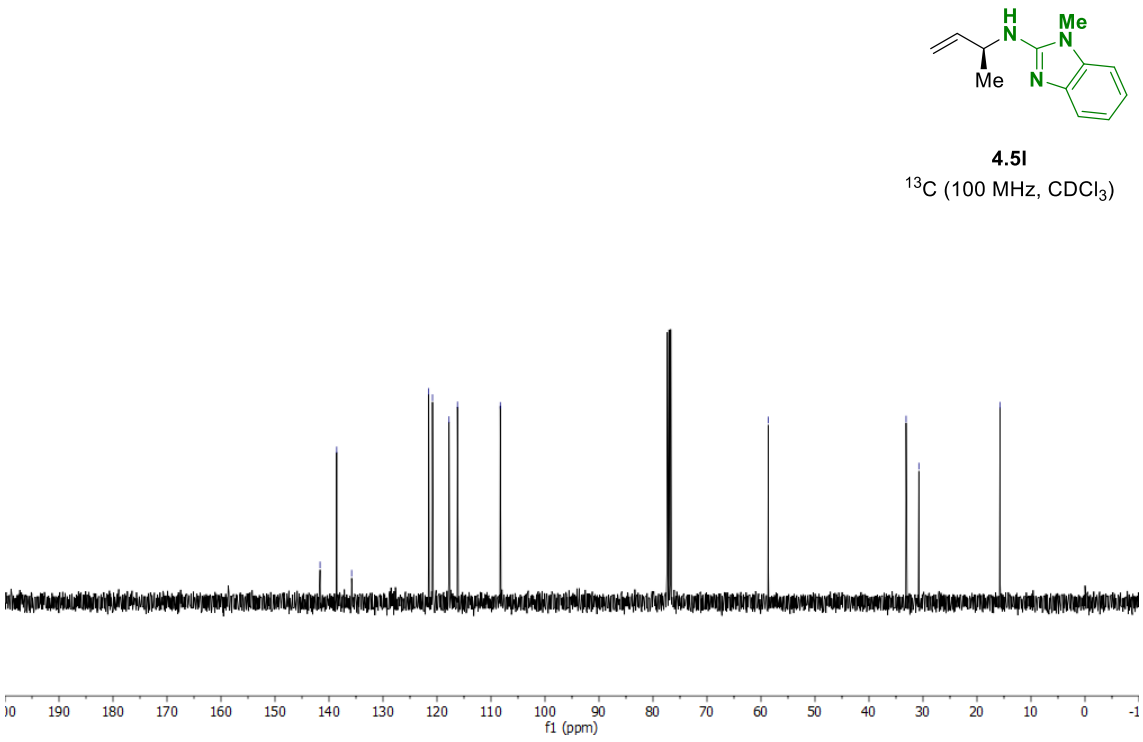
$[\alpha]_D^{28}$= –129.9 (*c* 0.2, $CHCl_3$).

HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 95:5, 1.00 mL/min, 254 nm), *ee* = 87%.



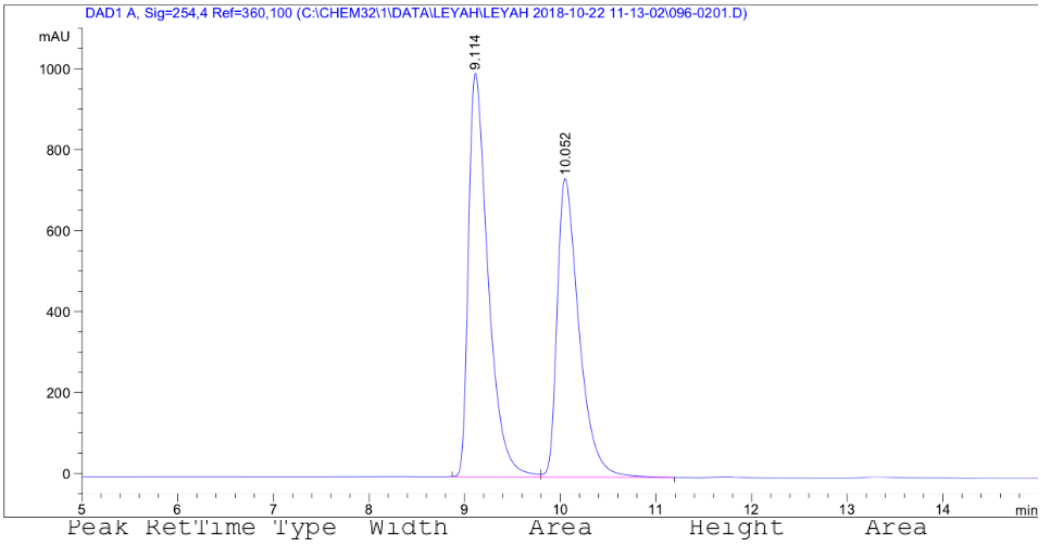
4.5l

^{1}H (400 MHz, $CDCl_3$)

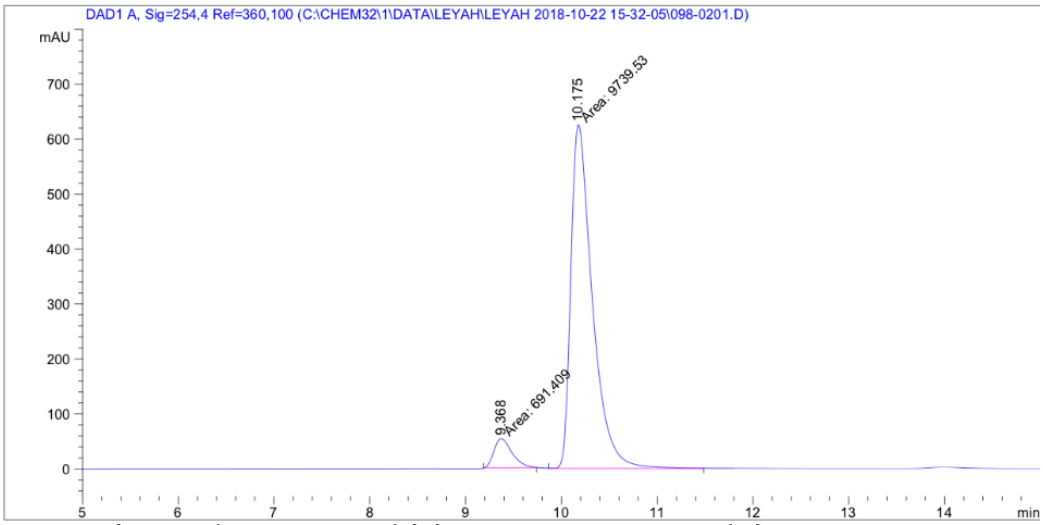


4.5l

^{13}C (100 MHz, $CDCl_3$)

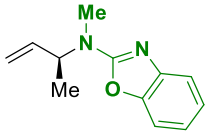


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.114	BV	0.2144	1.42238e4	997.30060	54.8302
2	10.052	VB	0.2394	1.17178e4	737.44312	45.1698



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.368	MM	0.2172	691.40906	53.04517	6.6284
2	10.175	MM	0.2597	9739.53223	625.12000	93.3716

(*S*)-N-(but-3-en-2-yl)-N-methylbenzo[d]oxazol-2-amine (4.6a)



4.6a

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 94% yield (83.7 mg, 0.41 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, heptanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.63 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.03 – 6.96 (m, 1H), 5.91 (ddd, *J* = 17.3, 10.7, 4.5 Hz, 1H), 5.28 – 5.20 (m, 2H), 5.04 (dqd, *J* = 8.8, 6.4, 5.6, 2.0 Hz, 1H), 3.02 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H).

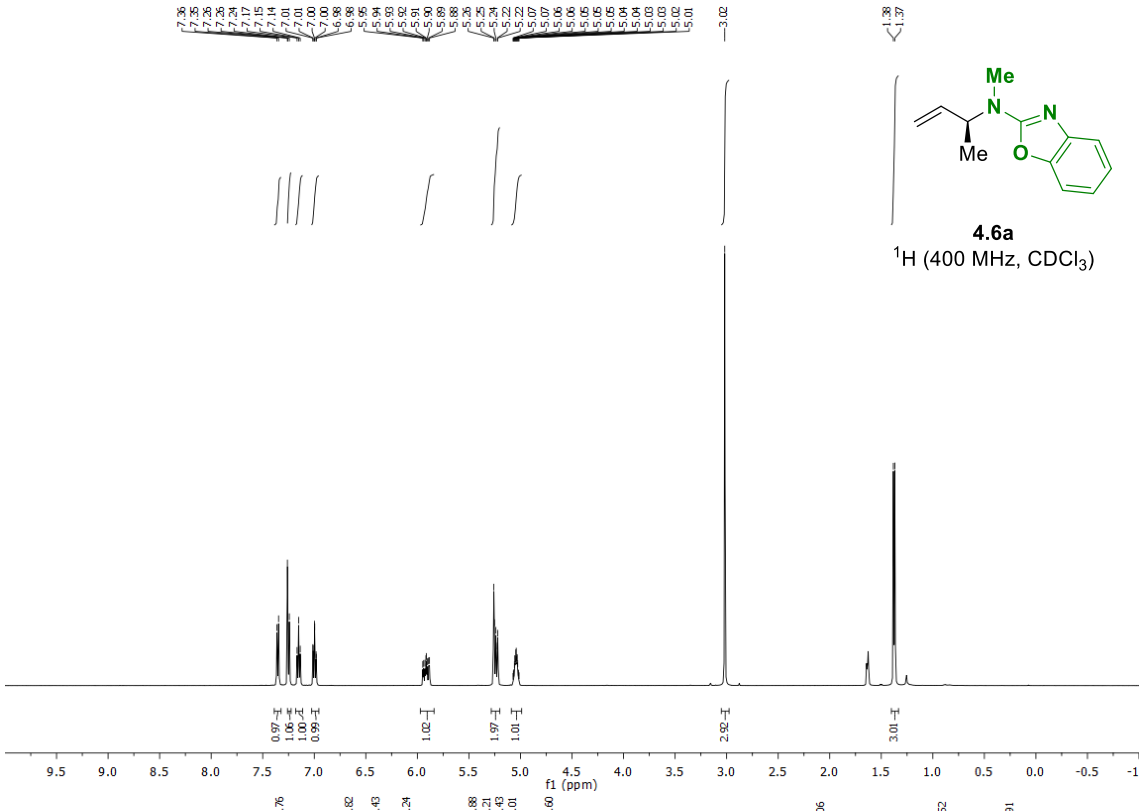
^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 148.8, 143.4, 137.2, 123.9, 120.2, 116.4, 116.0, 108.6, 54.1, 29.5, 15.9.

HRMS (ESI): Calculated for $C_{12}H_{14}N_2O$ [M+H$^+$] = 203.1179, Found 203.1180.

FTIR (neat): 2975, 1632, 1575, 1459, 1424, 1246, 1127, 1001, 925, 793, 740 cm^{-1}.

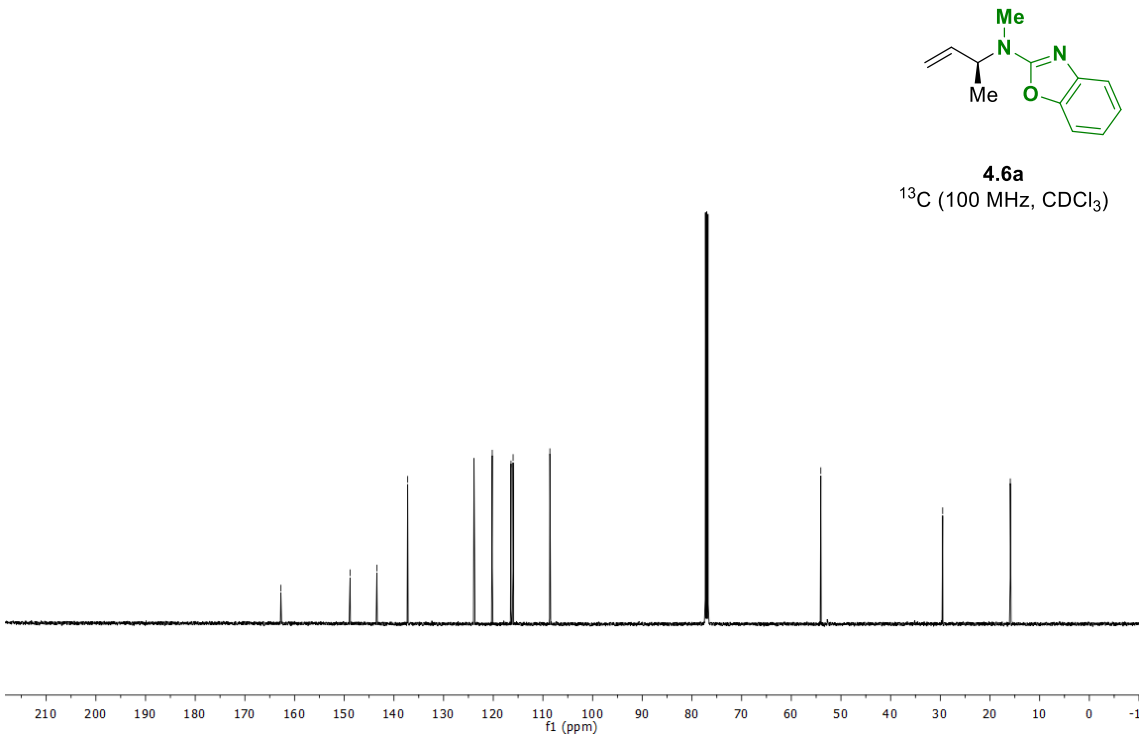
$[\alpha]_D^{28}$= –94.5 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 98:2, 1.00 mL/min, 254 nm), *ee* = 91%.



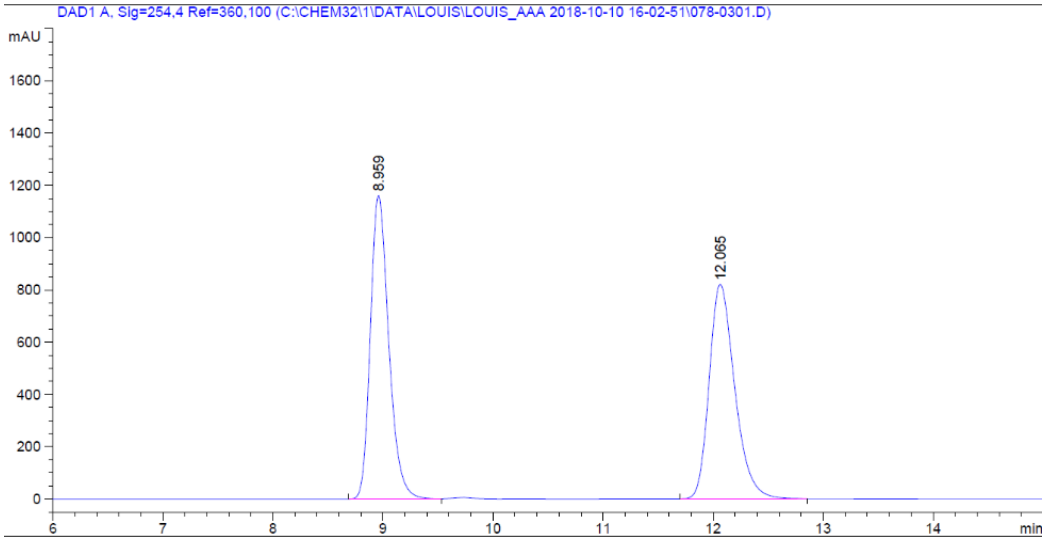
4.6a

^{1}H (400 MHz, $CDCl_3$)

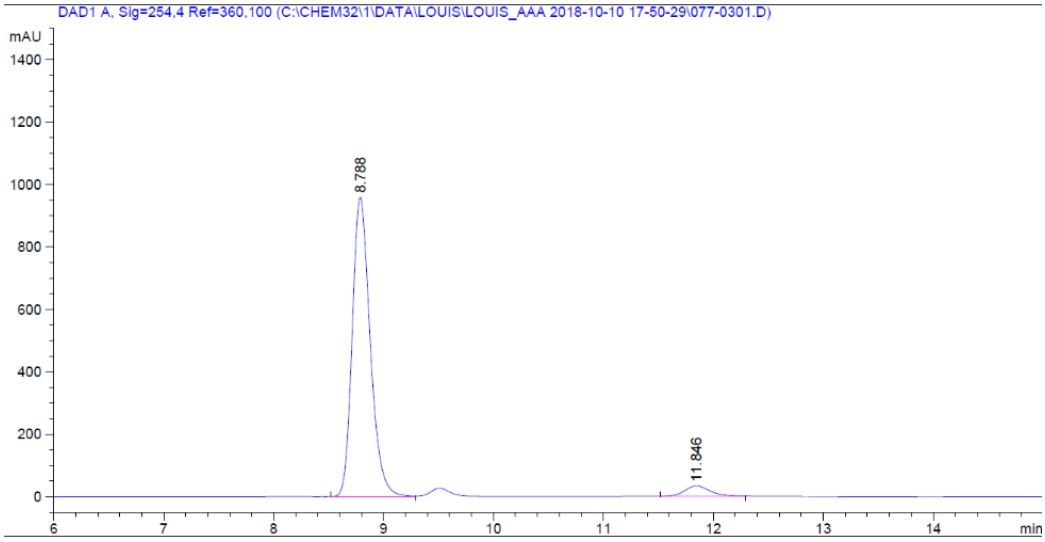


4.6a

^{13}C (100 MHz, $CDCl_3$)

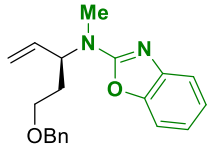


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.959	BV	0.1776	1.35025e4	1161.68359	50.4440
2	12.065	BB	0.2465	1.32648e4	820.81213	49.5560



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.788	BV	0.1742	1.08714e4	959.04358	95.3952
2	11.846	BB	0.2421	524.76575	33.25109	4.6048

(*S*)-N-(5-(benzyloxy)pent-1-en-3-yl)-N-methylbenzo[d]oxazol-2-amine (4.6b)



4.6b

The allylic acetate (103.1 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 93% yield (131.9 mg, 0.41 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.44 (hexanes: ethyl acetate = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 – 7.37 (m, 1H), 7.30 – 7.23 (m, 6H), 7.19 (td, *J* = 7.7, 1.1 Hz, 1H), 7.03 (td, *J* = 7.7, 1.2 Hz, 1H), 5.92 (ddd, *J* = 17.6, 10.4, 5.2 Hz, 1H), 5.30 – 5.27 (m, 1H), 5.25 (dt, *J* = 3.5, 1.3 Hz, 1H), 5.07 (ddd, *J* = 13.2, 7.0, 3.6 Hz, 1H), 4.44 (d, *J* = 2.8 Hz, 2H), 3.58 (dt, *J* = 9.5, 5.8 Hz, 1H), 3.52 (dt, *J* = 9.4, 6.7 Hz, 1H), 3.06 (s, 3H), 2.15 – 2.00 (m, 2H).

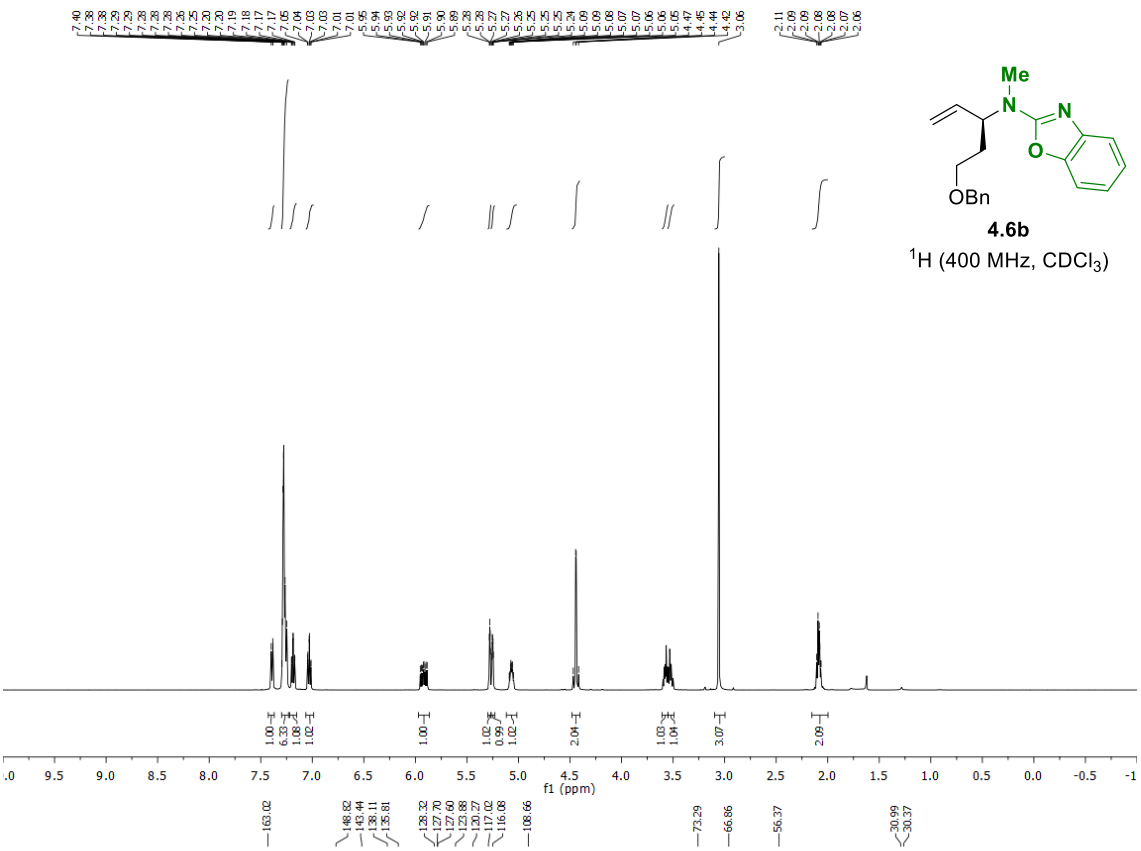
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 148.8, 143.4, 138.1, 135.8, 128.3, 127.7, 127.6, 123.9, 120.3, 117.0, 116.1, 108.7, 73.3, 66.9, 56.4, 31.0, 30.4.

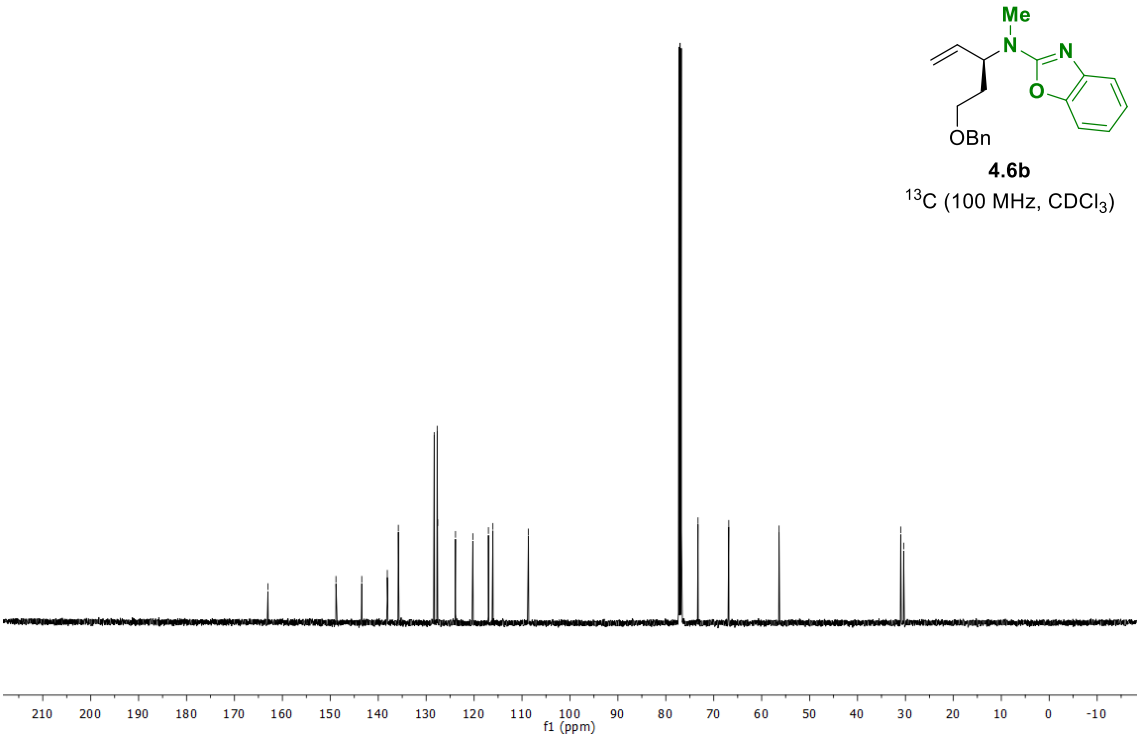
HRMS (ESI): Calculated for $C_{20}H_{22}N_2O_2$ [M+H$^+$] = 323.1754, Found 323.1757.

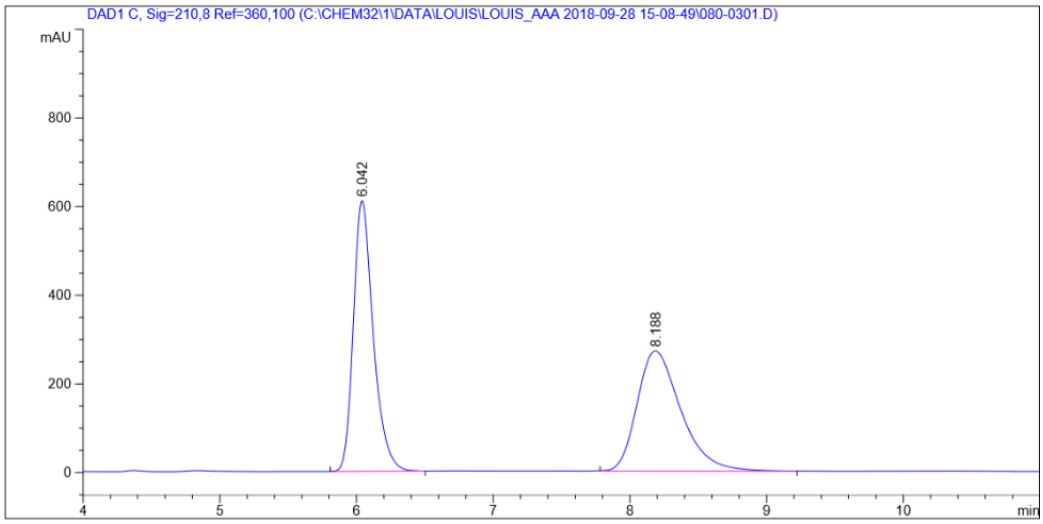
FTIR (neat): 2857, 1631, 1575, 1459, 1414, 1284, 1246, 1098, 1002, 907, 736, 697 cm^{-1}.

$[\alpha]_D^{28}$= –78.3 (*c* 1.0, $CHCl_3$).

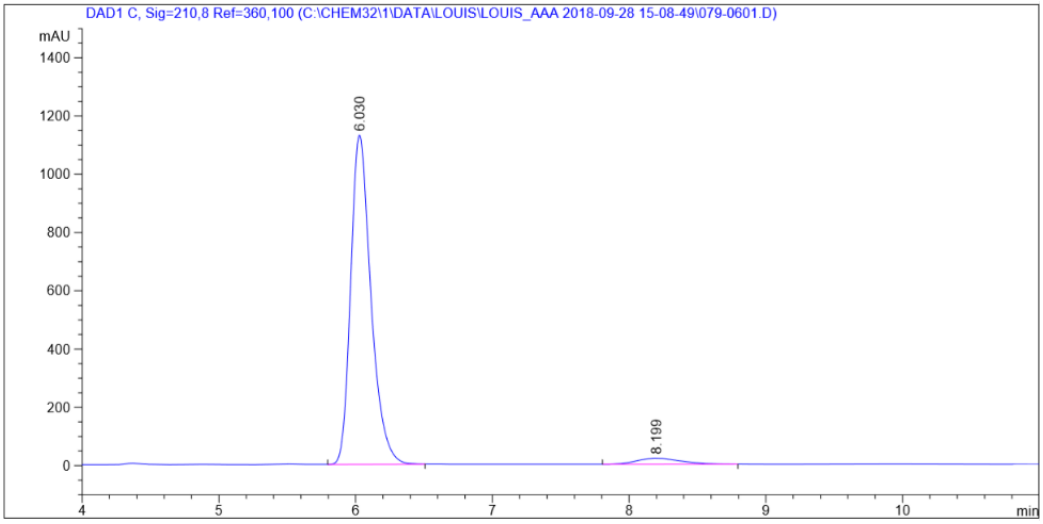
HPLC (Chiralcel AS-H column, hexanes:*i*-PrOH = 98:2, 1.00 mL/min, 210 nm), *ee* = 92%.


Me
N
N
O
OBn
4.6b
1H (400 MHz, CDCl3)
f1 (ppm)


Me
N
N
O
OBn
4.6b
13C (100 MHz, CDCl3)
f1 (ppm)

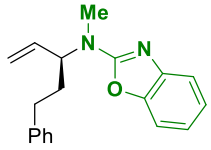


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.042	BB	0.1517	6161.05078	610.68341	50.5683
2	8.188	BB	0.3392	6022.58301	271.04453	49.4317



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.030	BB	0.1580	1.16281e4	1130.74524	96.1479
2	8.199	BB	0.3410	465.86823	20.98823	3.8521

(*S*)-N-methyl-N-(5-phenylpent-1-en-3-yl)benzo[d]oxazol-2-amine (4.6c)



4.6c

The allylic acetate (89.8 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 92% yield (118.3 mg, 0.40 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.44 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.24 – 7.14 (m, 4H), 7.04 (td, *J* = 7.8, 1.2 Hz, 1H), 5.91 (ddd, *J* = 17.6, 10.3, 5.2 Hz, 1H), 5.29 (t, *J* = 1.4 Hz, 1H), 5.26 (dt, *J* = 5.2, 1.3 Hz, 1H), 4.94 – 4.85 (m, 1H), 3.08 (s, 3H), 2.70 (t, *J* = 8.0 Hz, 2H), 2.15 – 2.00 (m, 2H).

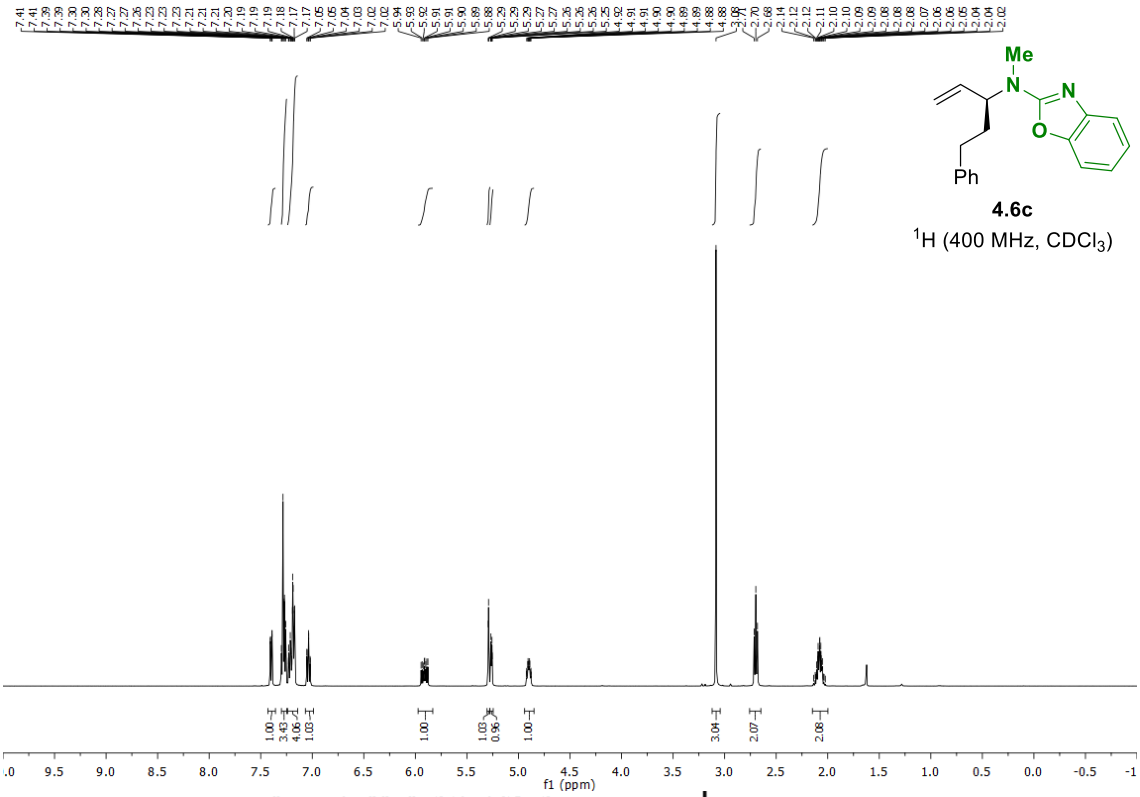
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 148.8, 143.4, 141.2, 135.8, 128.5, 128.3, 126.1, 123.9, 120.3, 117.1, 116.1, 108.7, 58.7, 32.8, 32.5, 29.8.

HRMS (ESI): Calculated for $C_{19}H_{20}N_2O$ [M+H$^+$] = 293.1648, Found 293.1656.

FTIR (neat): 2941, 1630, 1574, 1496, 1458, 1245, 1125, 1000, 926, 738, 698 cm^{-1}.

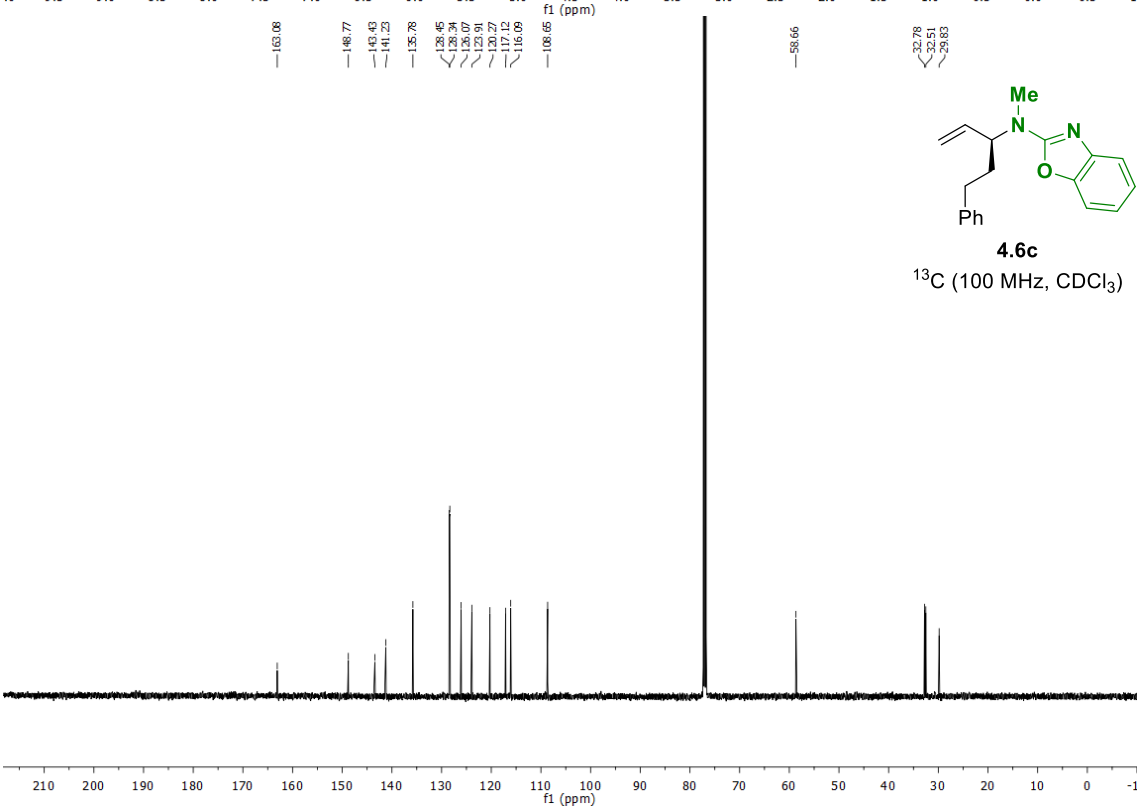
$[\alpha]_D^{28}$= –29.5 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 92%.



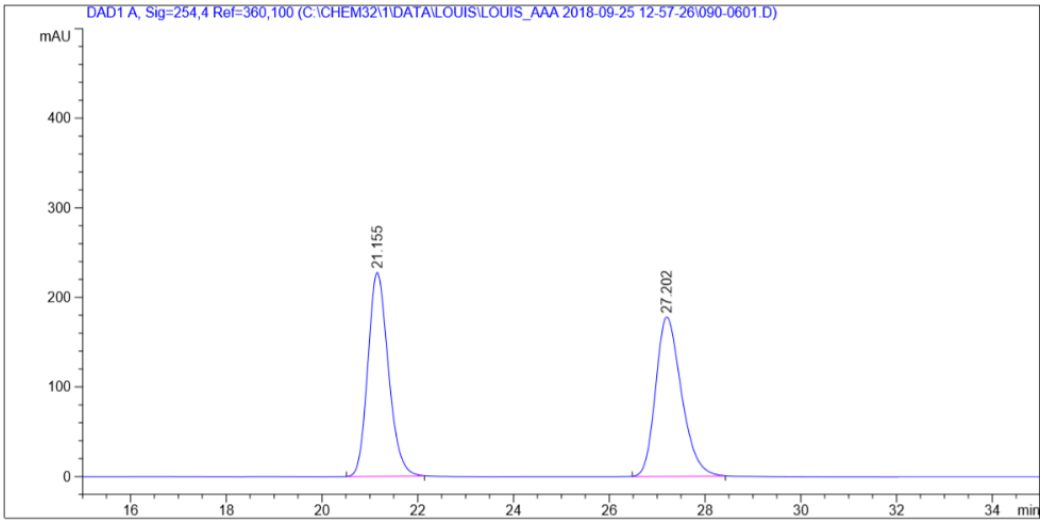
4.6c

^{1}H (400 MHz, $CDCl_3$)

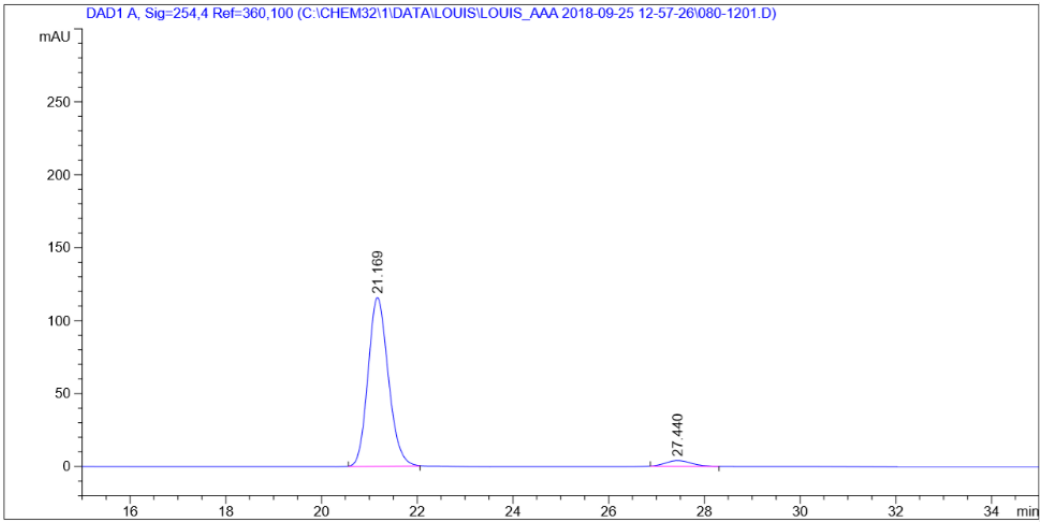


4.6c

^{13}C (100 MHz, $CDCl_3$)

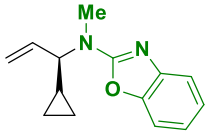


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.155	BB	0.4589	6768.60742	227.63060	50.3637
2	27.202	BB	0.5754	6670.84033	177.91081	49.6363



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.169	BB	0.4553	3404.30225	115.69923	95.9147
2	27.440	BB	0.4669	144.99965	3.98118	4.0853

(*R*)-N-(1-cyclopropylallyl)-N-methylbenzo[d]oxazol-2-amine (4.6d)



4.6d

The allylic acetate (61.7 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 48 hr). The title compound was obtained in 81% yield (81.3 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 30:1–15:1).

TLC (SiO_2) R_f = 0.56 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 6.99 (td, *J* = 7.8, 1.3 Hz, 1H), 5.93 (ddd, *J* = 17.4, 10.5, 4.4 Hz, 1H), 5.36 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.26 (dt, *J* = 10.5, 1.6 Hz, 1H), 4.16 – 4.04 (m, 1H), 3.16 (s, 3H), 1.14 (dtt, *J* = 9.6, 8.0, 4.9 Hz, 1H), 0.74 (dddd, *J* = 8.0, 6.7, 4.7, 3.3 Hz, 1H), 0.54 (tdd, *J* = 10.2, 4.3, 3.2 Hz, 1H), 0.48 – 0.35 (m, 2H).

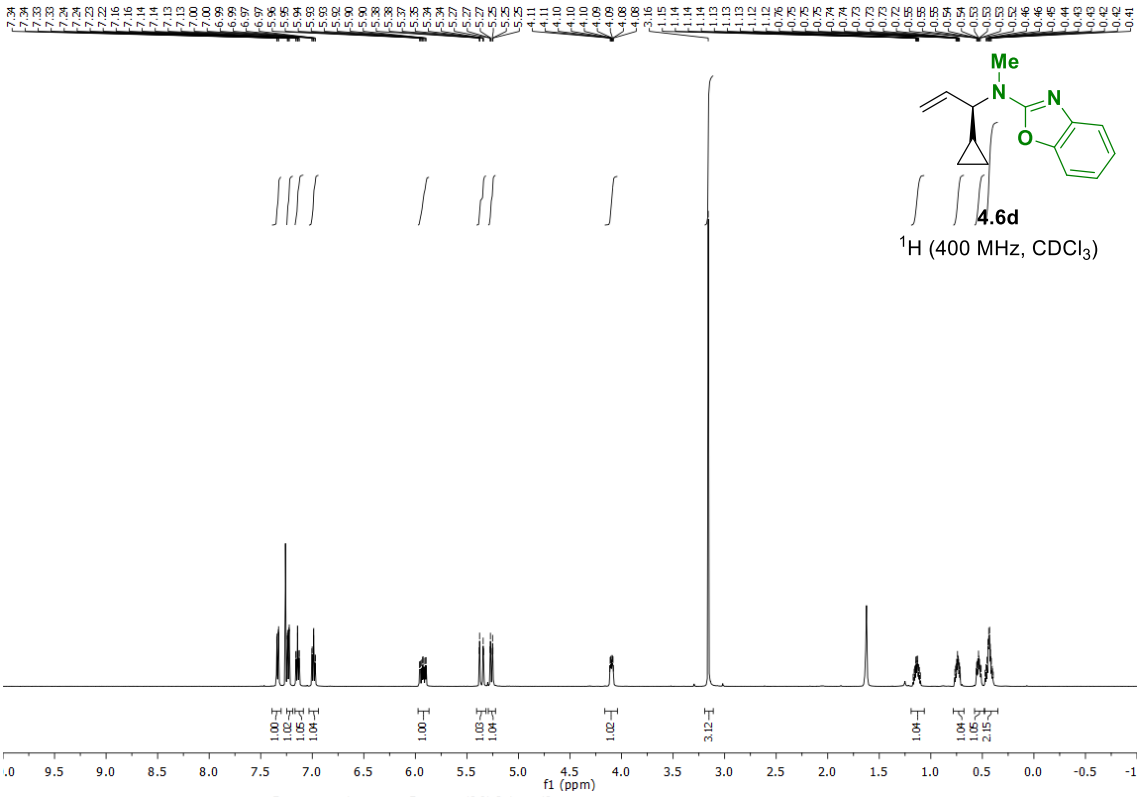
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 148.7, 143.5, 135.5, 123.9, 120.1, 116.9, 115.9, 108.6, 64.2, 30.6, 12.2, 5.0, 3.0.

HRMS (ESI): Calculated for $C_{14}H_{16}N_2O$ [M+H$^+$] = 229.1335, Found 229.1337.

FTIR (neat): 3007, 1629, 1573, 1458, 1423, 1245, 1124, 992, 908, 815, 738 cm^{-1}.

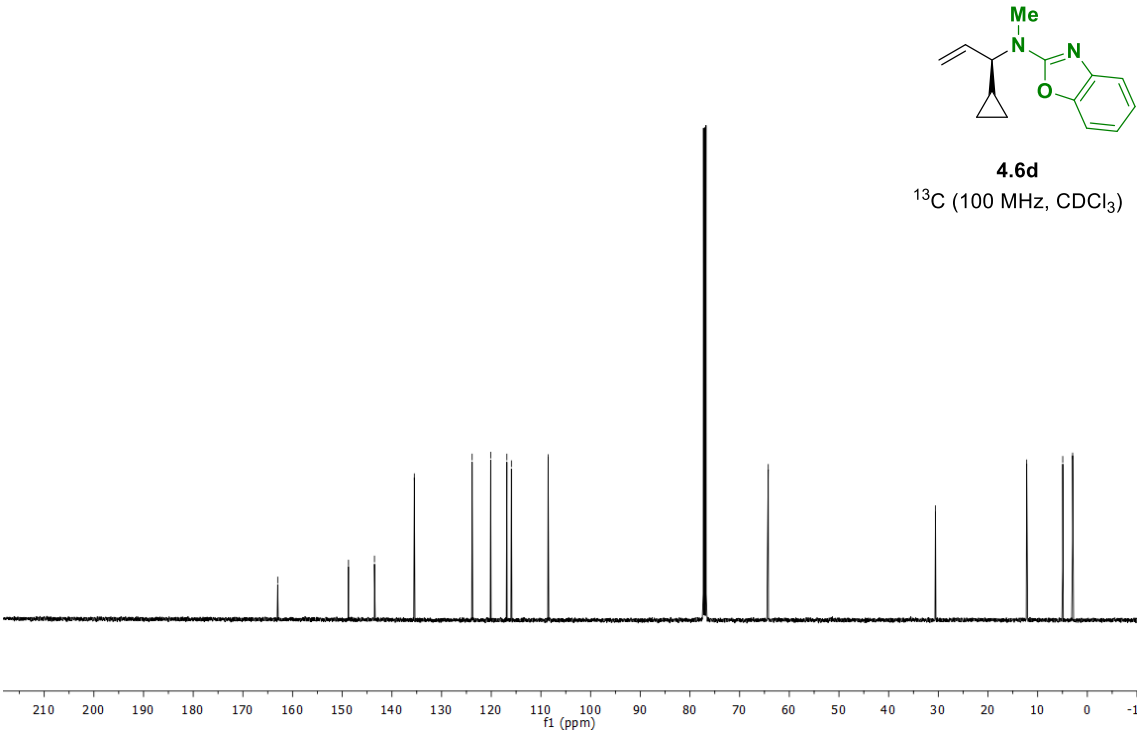
$[\alpha]_D^{28}$= –35.3 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 1.00 mL/min, 254 nm), *ee* = 90%.



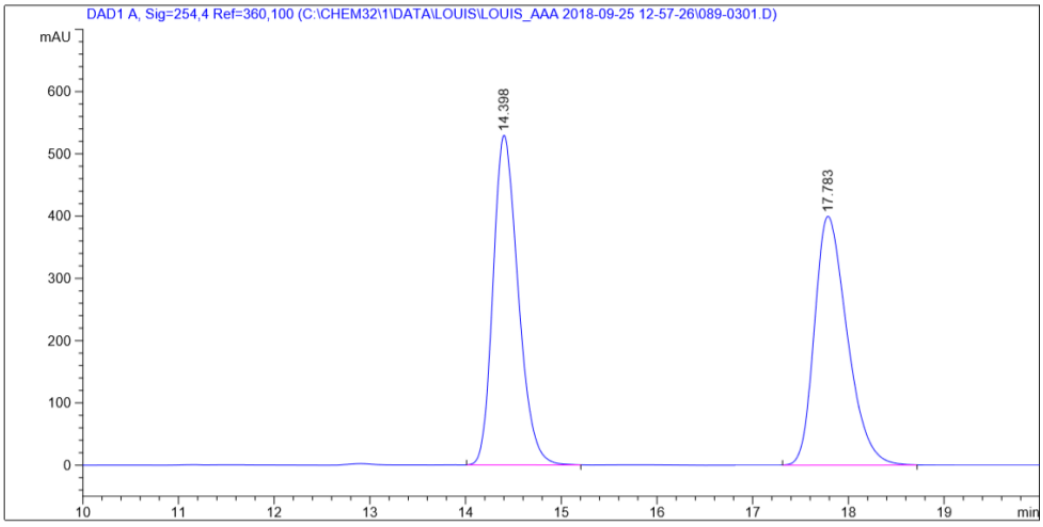
4.6d

^{1}H (400 MHz, $CDCl_3$)

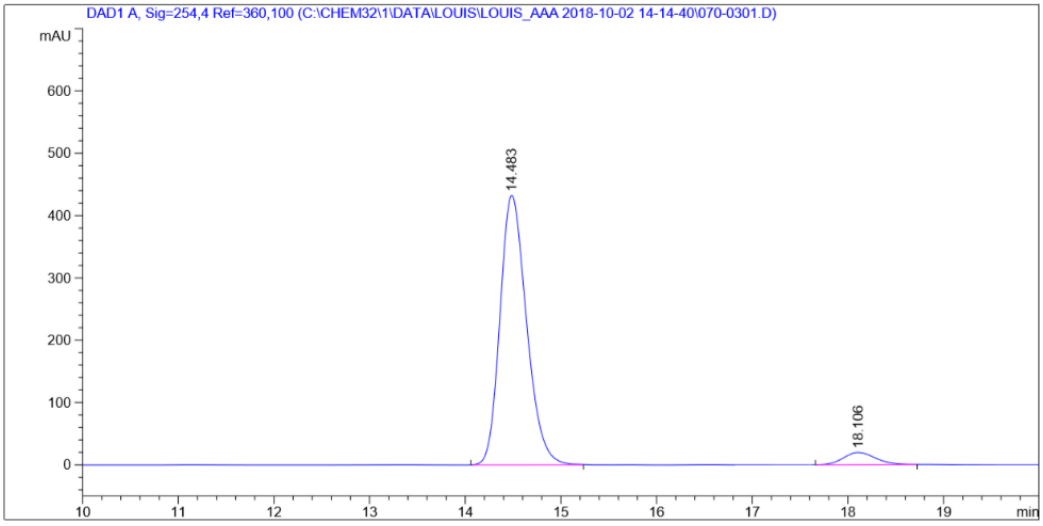


4.6d

^{13}C (100 MHz, $CDCl_3$)

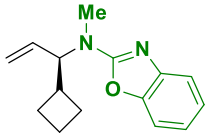


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.398	BB	0.2802	9628.84277	529.48486	50.3624
2	17.783	BB	0.3651	9490.25781	399.62079	49.6376



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.483	BB	0.2968	8335.59668	432.53293	94.8171
2	18.106	BB	0.3575	455.64526	19.72274	5.1829

(*R*)-N-(1-cyclobutylallyl)-N-methylbenzo[d]oxazol-2-amine (4.6e)



4.6e

The allylic acetate (67.9 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 48 hr). The title compound was obtained in 71% yield (75.7 mg, 0.31 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.44 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.32 (m, 1H), 7.25 (d, *J* = 5.9 Hz, 1H), 7.15 (td, *J* = 7.7, 1.2 Hz, 1H), 7.00 (td, *J* = 7.7, 1.3 Hz, 1H), 5.79 (ddd, *J* = 17.4, 10.7, 5.2 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.82 – 4.69 (m, 1H), 2.99 (s, 3H), 2.71 (dq, *J* = 11.0, 7.7 Hz, 1H), 2.15 (dt, *J* = 12.6, 7.7 Hz, 1H), 2.05 – 1.77 (m, 5H).

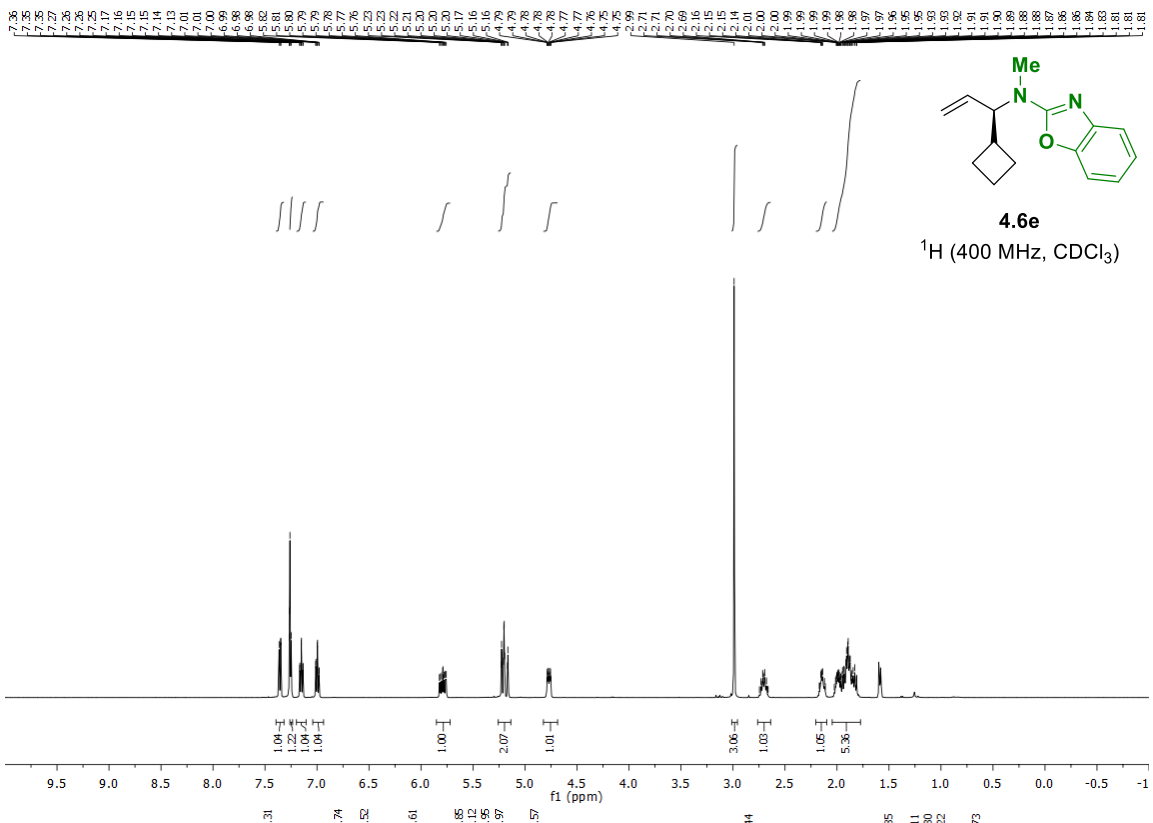
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 148.7, 143.5, 133.6, 123.9, 120.1, 117.0, 116.0, 108.6, 64.4, 35.9, 30.1, 26.3, 25.2, 17.7.

HRMS (ESI): Calculated for $C_{15}H_{18}N_2O$ [M+H$^+$] = 243.1492, Found 243.1495.

FTIR (neat): 2938, 1629, 1573, 1458, 1416, 1245, 1122, 990, 917, 821, 738 cm^{-1}.

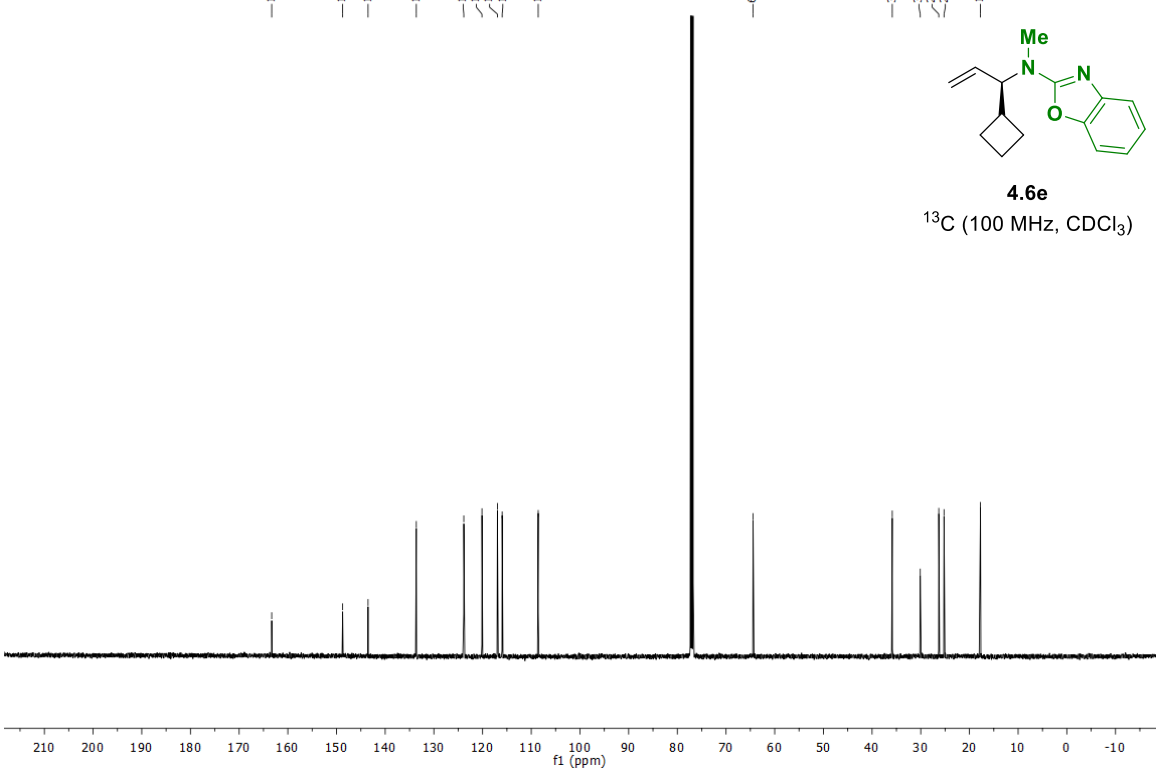
$[\alpha]_D^{28}$= –98.8 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 98:2, 1.00 mL/min, 210 nm), *ee* = 90%.



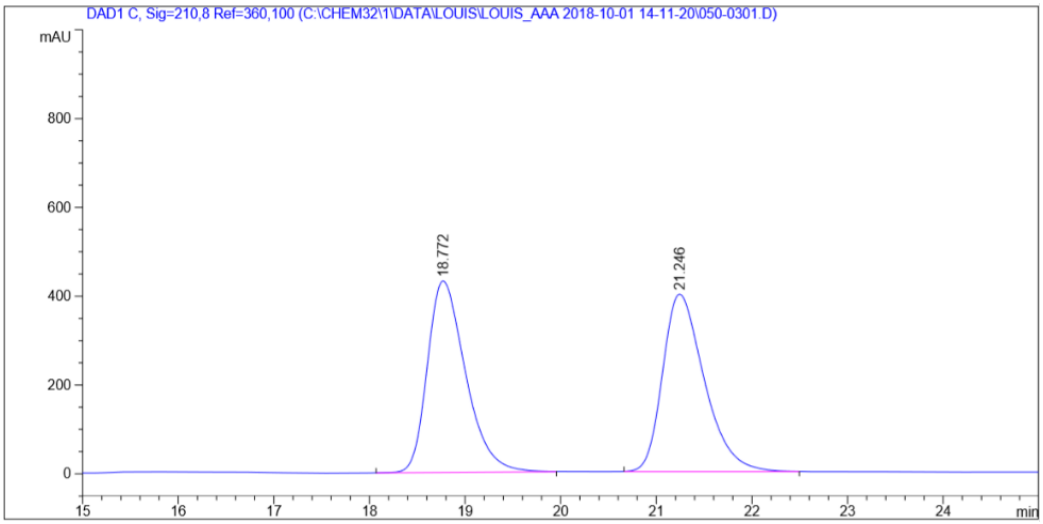
4.6e

^{1}H (400 MHz, $CDCl_3$)

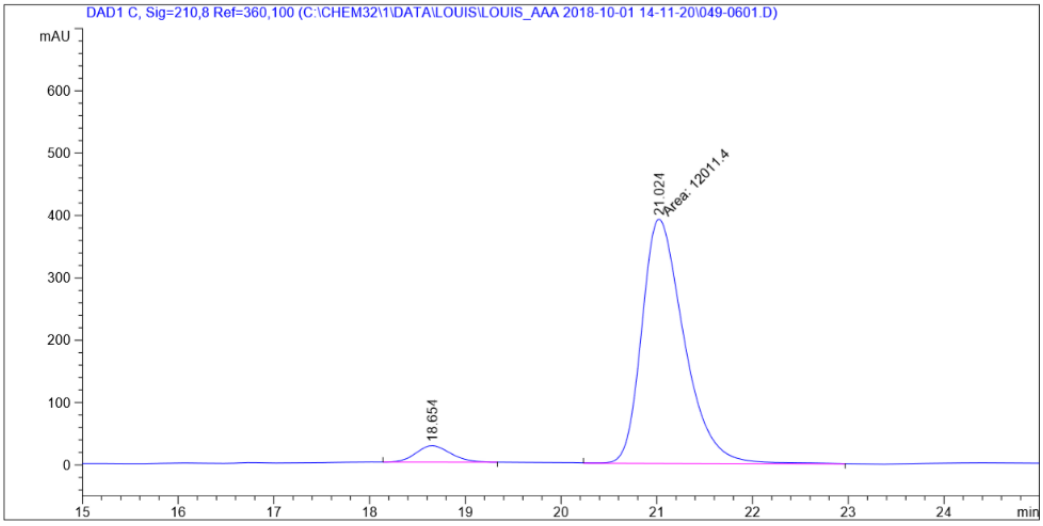


4.6e

^{13}C (100 MHz, $CDCl_3$)

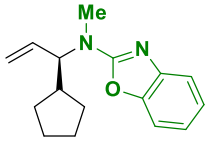


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.772	BB	0.4275	1.19520e4	431.09497	49.6819
2	21.246	BB	0.4634	1.21050e4	399.59698	50.3181



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.654	BB	0.3952	664.82928	26.45481	5.2447
2	21.024	MM	0.5111	1.20114e4	391.67349	94.7553

(*R*)-N-(1-cyclopentylallyl)-N-methylbenzo[d]oxazol-2-amine (4.6f)



4.6f

The allylic acetate (74.0 mg, 0.44 mmol, 100 mol%) and the secondary amine (130.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 60 hr). The title compound was obtained in 81% yield (91.3 mg, 0.36 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 20:1–10:1).

TLC (SiO_2) R_f = 0.44 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.14 (td, *J* = 7.7, 1.2 Hz, 1H), 6.99 (td, *J* = 7.7, 1.2 Hz, 1H), 5.89 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.30 – 5.18 (m, 2H), 4.56 – 4.45 (m, 1H), 3.06 (s, 3H), 2.25 (dp, *J* = 10.9, 8.0 Hz, 1H), 1.82 (dp, *J* = 12.5, 4.5, 3.8 Hz, 1H), 1.74 – 1.50 (m, 5H), 1.33 (dddd, *J* = 16.2, 10.9, 7.9, 2.4 Hz, 2H).

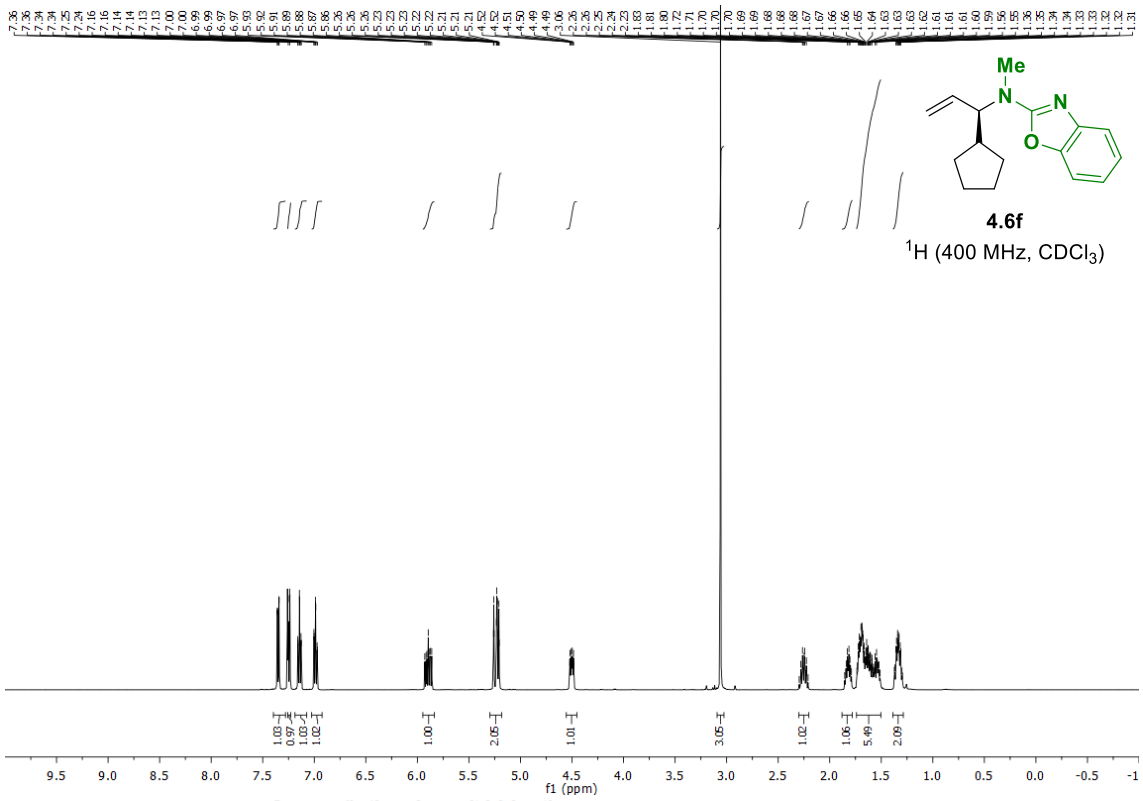
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 148.7, 143.6, 135.1, 123.8, 120.1, 117.3, 116.0, 108.6, 64.6, 41.0, 30.5, 30.3, 30.0, 25.6, 25.3.

HRMS (ESI): Calculated for $C_{16}H_{20}N_2O$ [M+H$^+$] = 257.1648, Found 257.1650.

FTIR (neat): 2951, 1629, 1573, 1458, 1245, 1123, 990, 921, 819, 738 cm^{-1}.

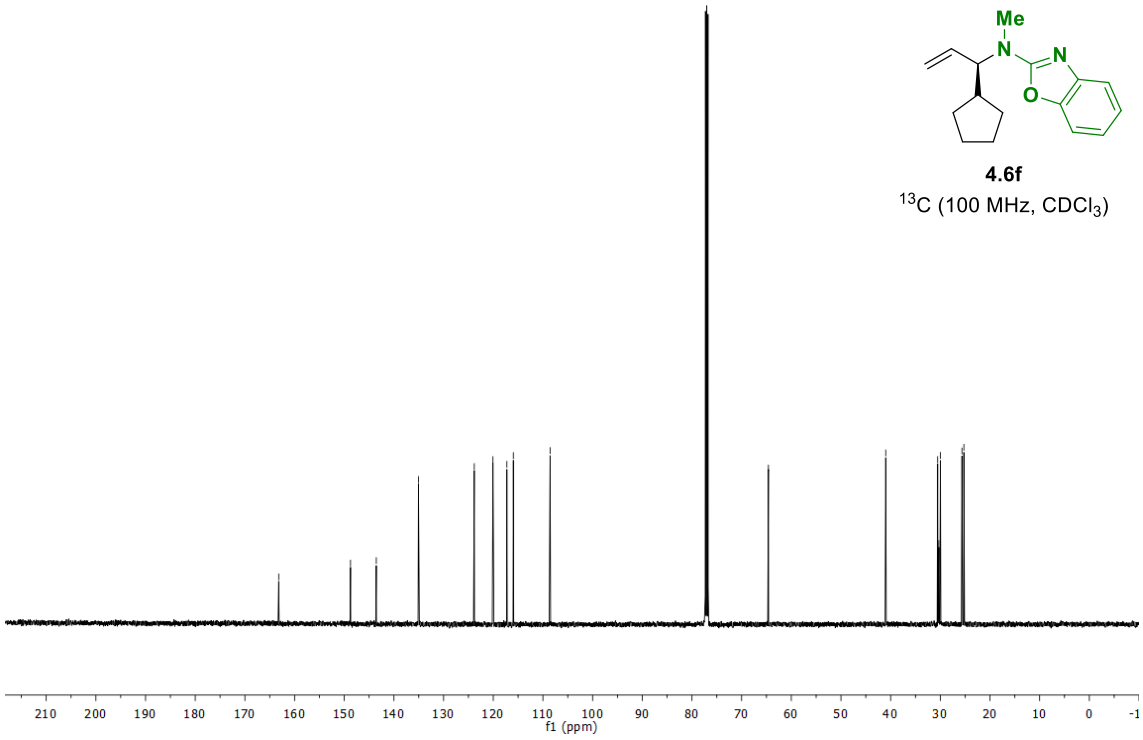
$[\alpha]_D^{28}$= –92.0 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, hexanes:*i*-PrOH = 97:3, 1.00 mL/min, 210 nm), *ee* = 85%.



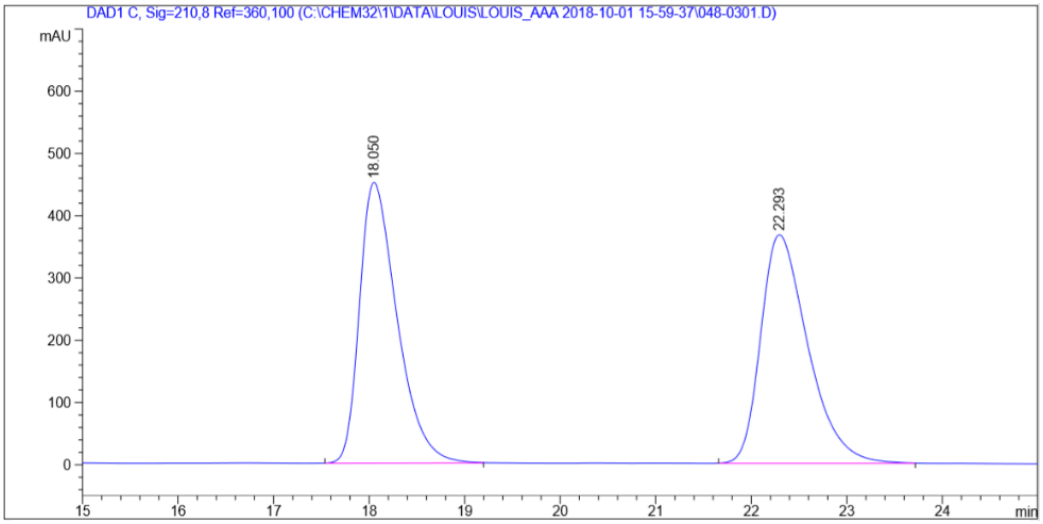
4.6f

^{1}H (400 MHz, $CDCl_3$)

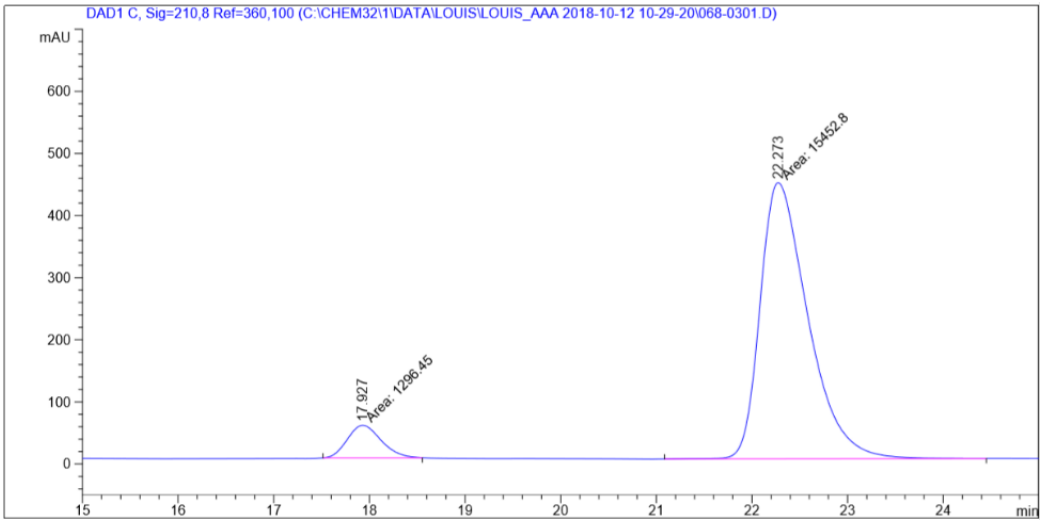


4.6f

^{13}C (100 MHz, $CDCl_3$)

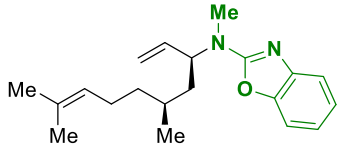


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.050	BB	0.4168	1.23153e4	450.69016	49.4850
2	22.293	BB	0.5236	1.25717e4	367.08105	50.5150



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.927	MM	0.4104	1296.45154	52.64453	7.7403
2	22.273	MM	0.5792	1.54528e4	444.68332	92.2597

***N*-((3*S*,5*S*)-5,9-dimethyldeca-1,8-dien-3-yl)-*N*-methylbenzo[*d*]oxazol-2-amine (4.6g)**



4.6g

The allylic acetate (98.7 mg, 0.44 mmol, 100 mol%) and the primary amine (130.4 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 60 hr). The title compound was obtained in 80% yield, 10:1 dr (110.2 mg, 0.35 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 10 min).

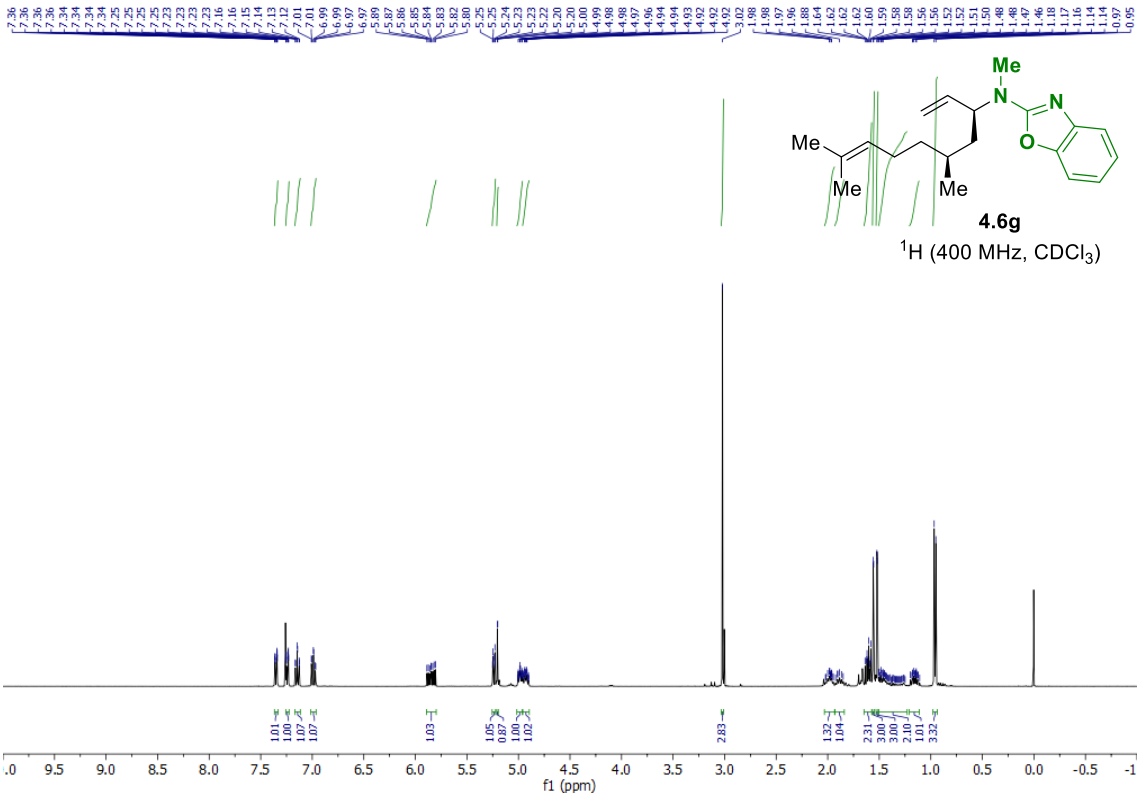
TLC (SiO_2) R_f = 0.33 (heptane: isopropyl acetate = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 1H), 7.24 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.14 (td, *J* = 7.7, 1.1 Hz, 1H), 6.99 (td, *J* = 7.7, 1.2 Hz, 1H), 5.85 (ddd, *J* = 172., 10.6, 5.4 Hz, 1H), 5.24 (dt, *J* = 7.5, 1.3 Hz, 1H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.99 (ddq, *J* = 8.5, 5.6, 1.4 Hz, 1H), 4.93 (dddt, *J* = 8.4, 6.9, 5.4, 1.6 Hz, 1H), 3.02 (s, 3H), 2.03-1.93 (m, 1H), 1.89 (dt, *J* = 14.7, 7.1 Hz, 1H), 1.65-1.57 (m, 2H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.52 (d, *J* = 1.3 Hz, 3H), 1.50-1.23 (m, 2H), 1.21-1.11 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 148.8, 143.6, 136.2, 131.4, 124.4, 123.8, 120.1, 116.8, 116.1, 108.6, 56.9, 38.5, 36.3, 29.9, 29.0, 25.5, 25.3, 20.0, 17.6.

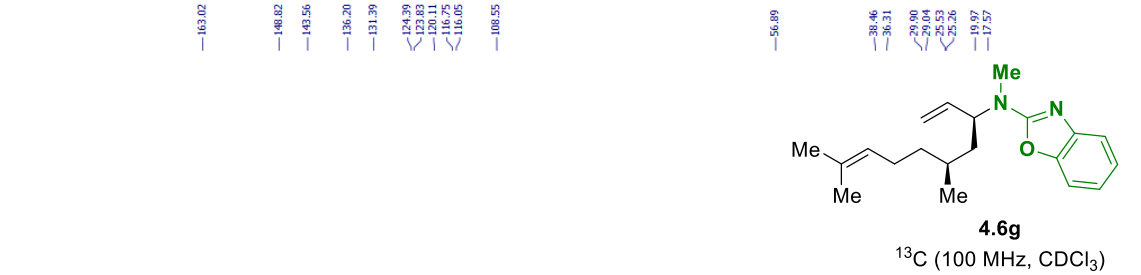
HRMS (ESI): Calculated for $C_{20}H_{28}N_2O$ [M+H$^+$] = 313.2274, Found 313.2276.

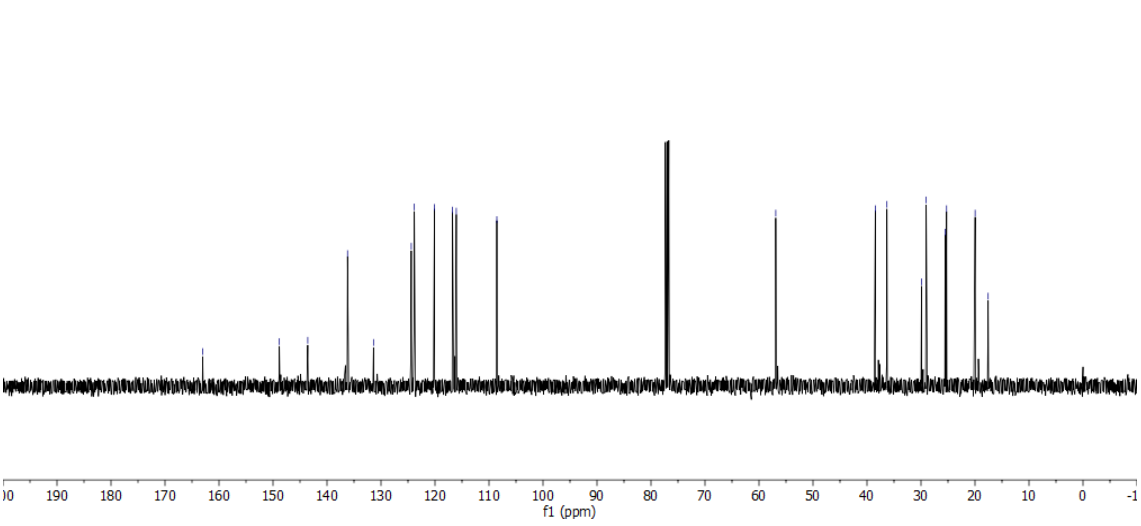
FTIR (neat): 3726, 2961, 2914, 2360, 2341, 1632, 1575, 1459, 1246, 1125, 922, 754, 739, 669, 429 cm^{-1}.



4.6g

^{1}H (400 MHz, $CDCl_3$)

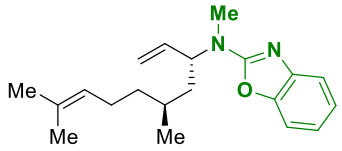




4.6g

^{13}C (100 MHz, $CDCl_3$)

***N*-((3*R*,5*S*)-5,9-dimethyldeca-1,8-dien-3-yl)-*N*-methylbenzo[*d*]oxazol-2-amine (*iso*-4.6g)**



iso-**4.6g**

The allylic acetate (98.7 mg, 0.44 mmol, 100 mol%) and the primary amine (130.4 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 60 hr) with (*R*)-Ir-II. The title compound was obtained in 76% yield, 20:1 dr (104.4 mg, 0.33 mmol) as a light yellow oil after purification by flash column chromatography (4g SiO_2, Isopropyl Acetate / Heptane = 0% - 10% over 10 min).

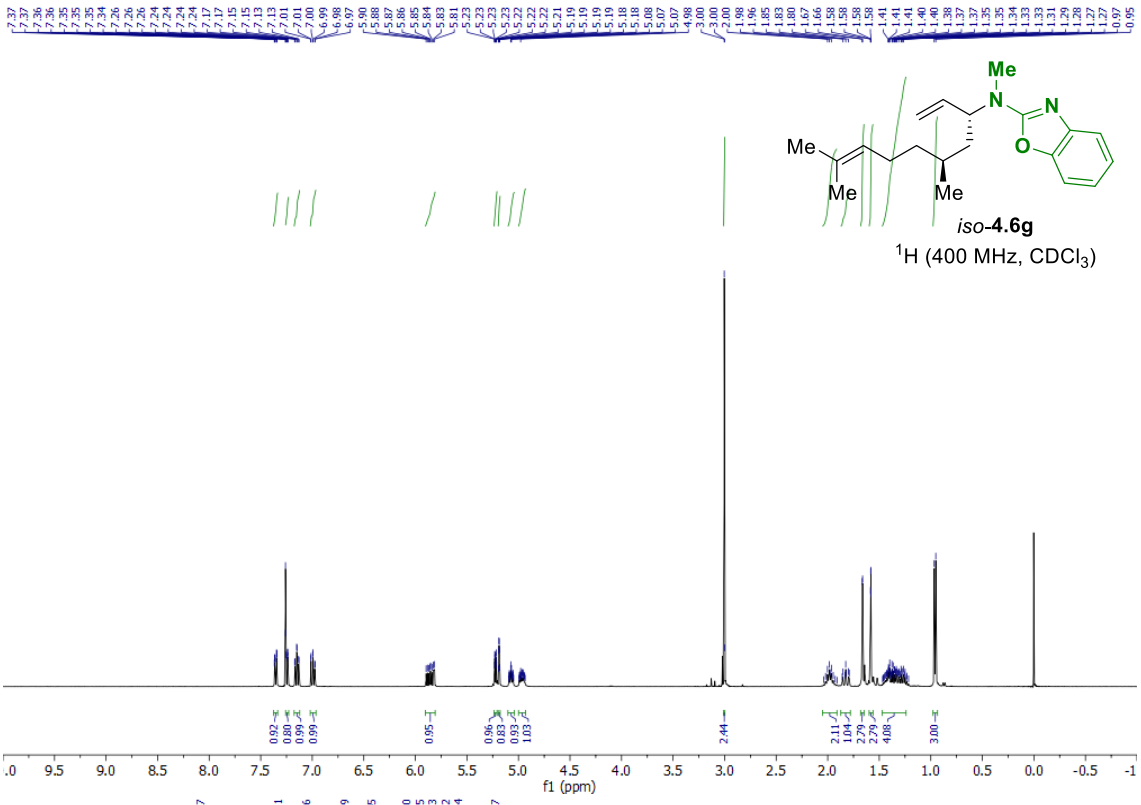
TLC (SiO_2) R_f = 0.33 (heptane: isopropyl acetate = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 1H), 7.26-7.23 (m, 1H), 7.15 (td, *J* =7.7, 1.2 Hz, 1H), 7.02-6.96 (m, 1H), 5.85 (ddd, *J* = 17.5, 10.4, 5.0 Hz, 1H), 5.22 (ddd, *J* = 5.3, 1.7, 1.2 Hz, 1H), 5.19 (td, *J* = 1.8, 1.2 Hz, 1H), 5.07 (ddq, *J* = 8.5, 5.7, 1.3 Hz, 1H), 4.97 (dtt, *J* = 11.1, 4.5, 1.7 Hz, 1H), 3.00 (s, 2H), 1.98 (p, *J* =7.3 Hz, 2H), 1.83 (ddd, *J* = 13.6, 10.9, 2.9 Hz, 1H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.60-1.56 (m, 3H), 1.47-1.24(m, 4H), 0.96 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 148.8, 143.6, 136.6, 131.5, 134.5, 123.9, 120.1, 116.3, 116.0, 108.6, 56.5, 37.9, 37.7, 29.6, 29.0, 25.7, 25.5, 19.4, 17.7.

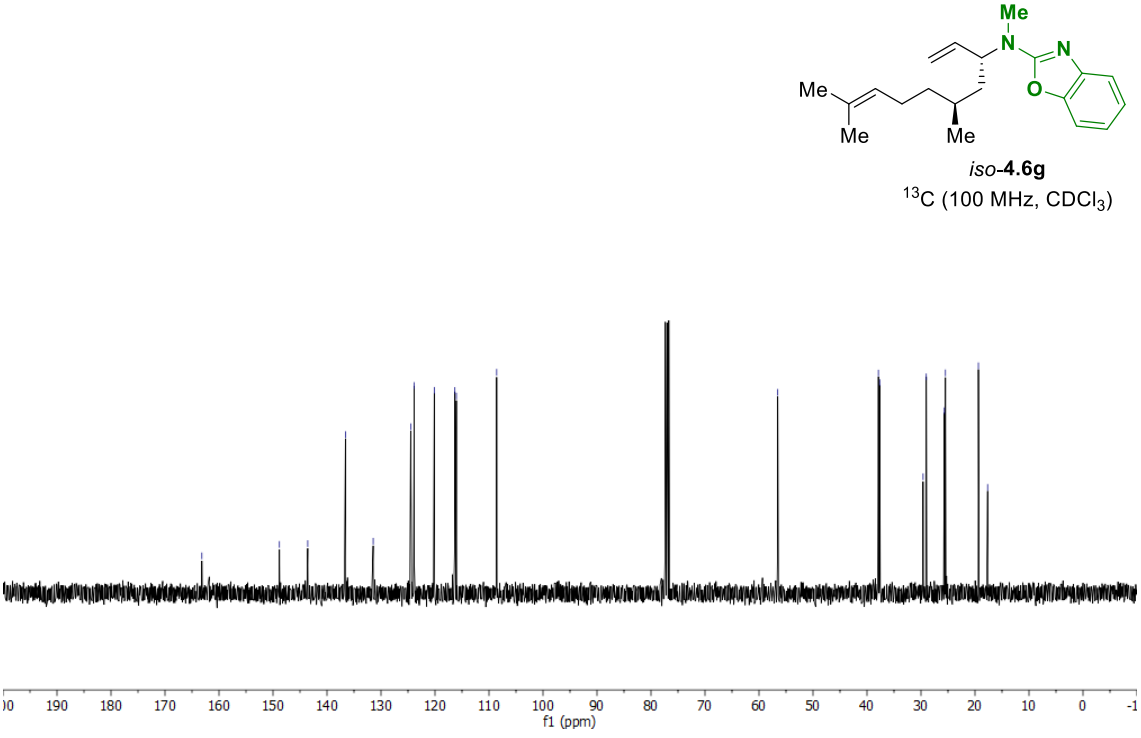
HRMS (ESI): Calculated for $C_{20}H_{28}N_2O$ [M+H$^+$] = 313.2274, Found 313.2278.

FTIR (neat): 2915, 2360, 2341, 1634, 1577, 1460, 1577, 1460, 1247, 924, 754, 740, 669, 650 cm^{-1}.



iso-**4.6g**

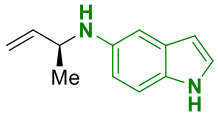
^{1}H (400 MHz, $CDCl_3$)



iso-**4.6g**

^{13}C (100 MHz, $CDCl_3$)

(*S*)-N-(but-3-en-2-yl)-1H-indol-5-amine (4.7a)



4.7a

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the amine (116.3 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 24 hr). The title compound was obtained in 91% yield (74.5 mg, 0.40 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 40% over 20 min).

TLC (SiO_2) R_f = 0.32 (heptanes: ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (br, 1H), 7.19 (dt, *J* = 8.6, 0.8 Hz, 1H), 7.12 – 7.08 (m, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.63 (ddd, *J* = 8.7, 2.3, 0.4 Hz, 1H), 6.39 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H), 5.90 (ddd, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.08 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.07 – 3.97 (m, 1H), 1.34 (d, *J* = 6.6 Hz, 3H).

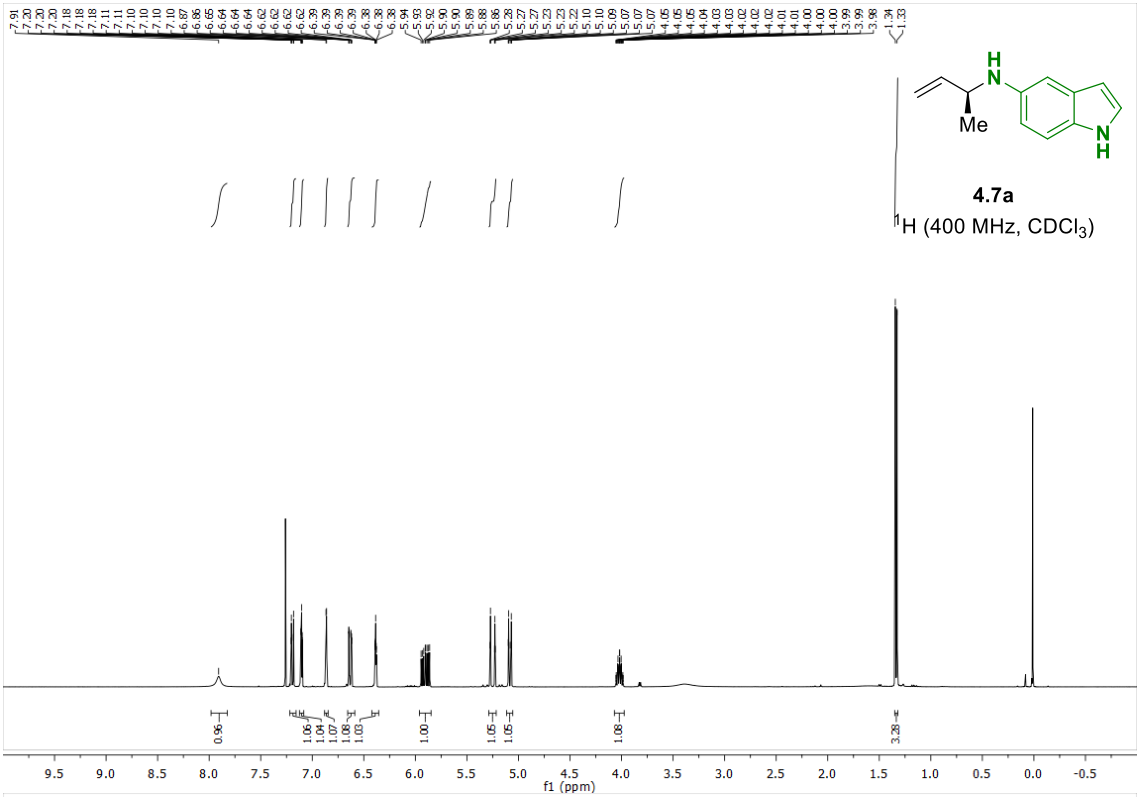
^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 141.4, 130.1, 128.8, 124.4, 113.9, 112.8, 111.5, 103.7, 101.8, 52.5, 21.7.

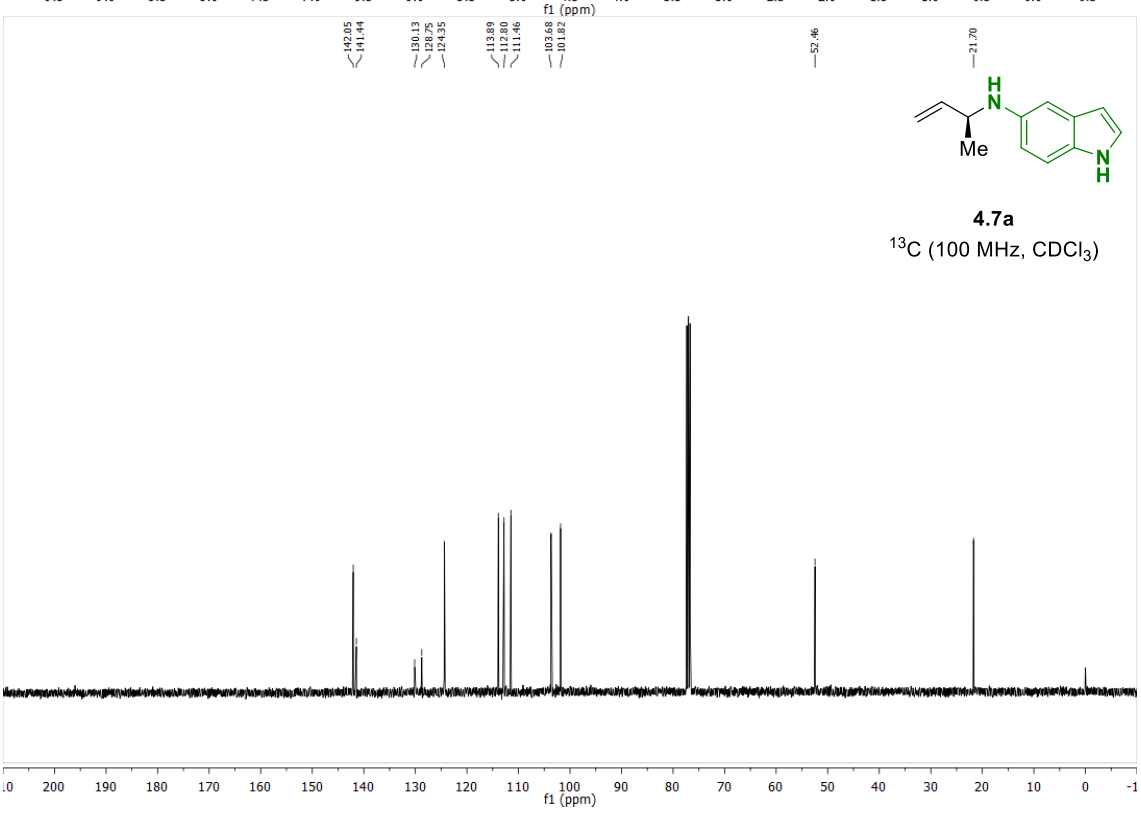
HRMS (ESI): Calculated for $C_{12}H_{15}N_2$ $[M+H^+]$ = 187.1230, Found 187.1230.

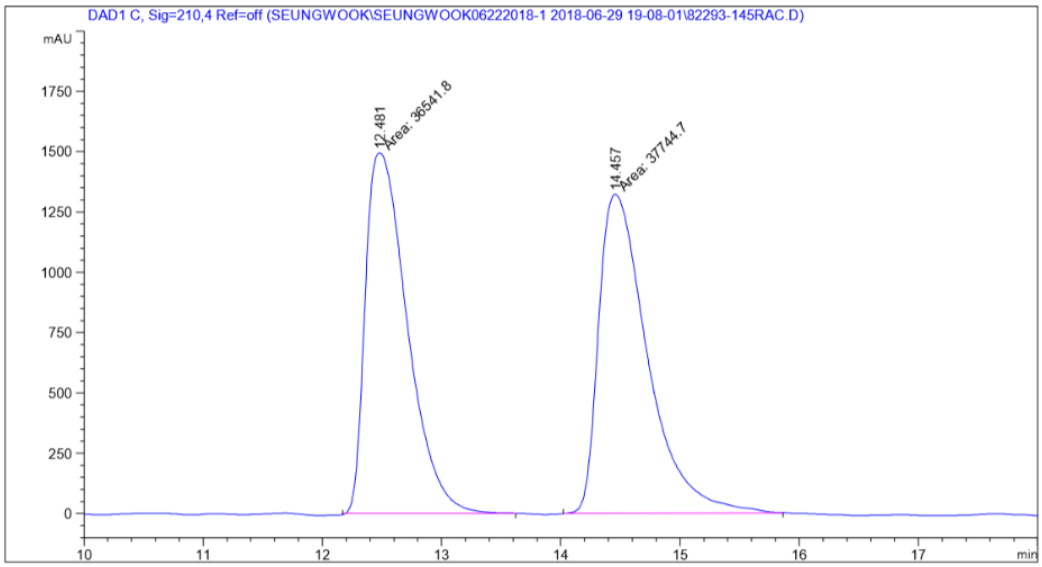
FTIR (neat): 3404, 2975, 1626, 1581, 1469, 1231, 1167, 919, 797, 724, 602 cm^{-1}.

$[\alpha]_D^{28}$ = –5.0 (*c* 0.2, $CHCl_3$).

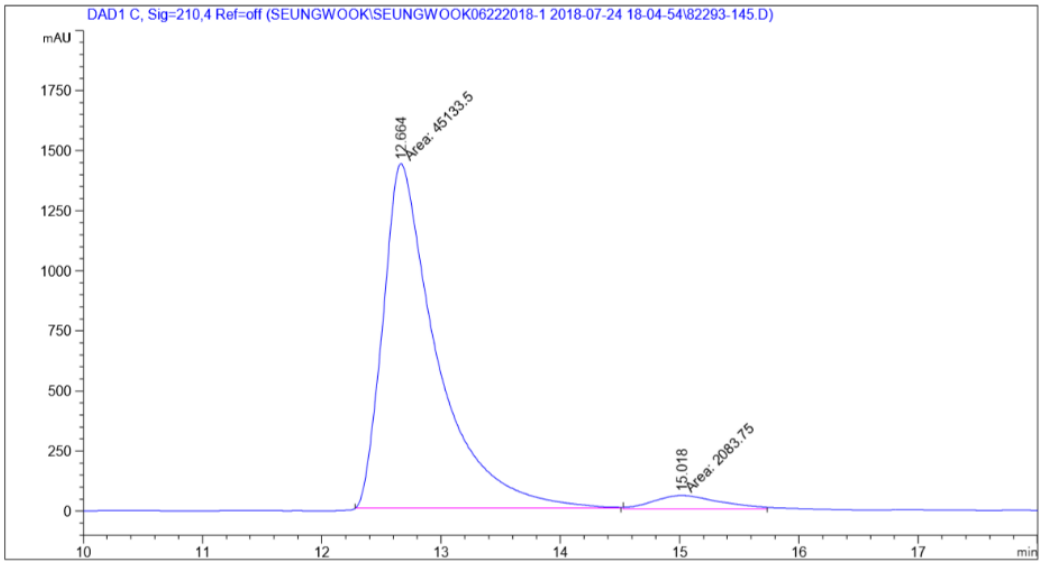
HPLC (Chiralcel OD-3 column, heptanes:*i*-PrOH = 80:20, 1.00 mL/min, 210 nm), *ee* = 91%.


Me
4.7a
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


Me
4.7a
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

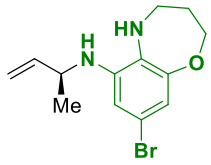


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.481	MM	0.4075	3.65418e4	1494.69006	49.1904
2	14.457	MM	0.4756	3.77447e4	1322.68848	50.8096



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.664	MM	0.5249	4.51335e4	1433.09302	95.5869
2	15.018	MM	0.6329	2083.75391	54.86946	4.4131

(*S*)-8-bromo-N-(but-3-en-2-yl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-6-amine (4.7b)



4.7b

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the amine (213.9 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (70 °C, 24 hr). The title compound was obtained in 61% yield (79.8 mg, 0.27 mmol) as a light yellow oil after purification by flash column chromatography (SiO_2, hexanes: ethyl acetate = 10:1–5:1).

TLC (SiO_2) R_f = 0.24 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.53 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.09 (dt, *J* = 10.3, 1.3 Hz, 1H), 4.50 (d, *J* = 6.3 Hz, 1H), 4.13 (t, *J* = 5.5 Hz, 2H), 3.85 (q, *J* = 6.3 Hz, 1H), 3.25 – 3.08 (m, 2H), 2.60 (br, 1H), 2.01 (ddd, *J* = 10.0, 6.5, 4.8 Hz, 2H), 1.31 (d, *J* = 6.6 Hz, 3H).

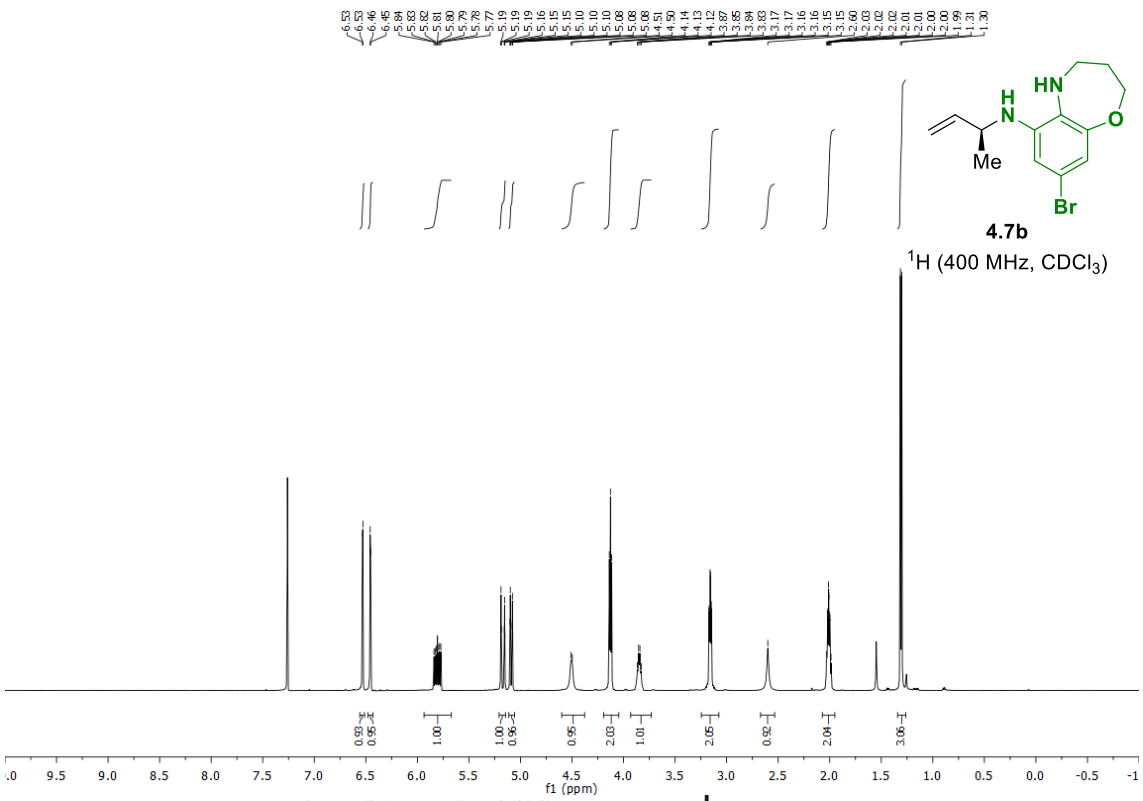
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 144.5, 140.8, 126.4, 116.5, 114.3, 113.5, 110.6, 71.9, 51.5, 45.6, 33.5, 21.6.

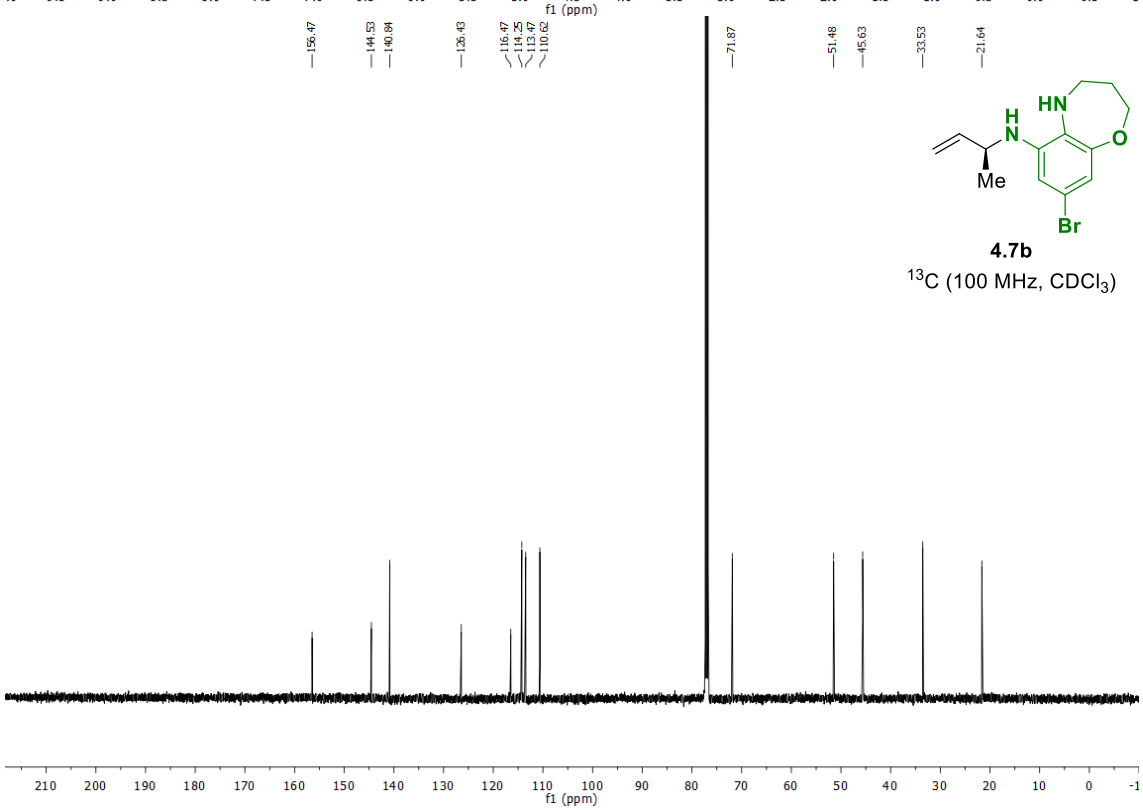
HRMS (ESI): Calculated for $C_{13}H_{17}BrN_2O$ [M+H$^+$] = 297.0597, Found 297.0581.

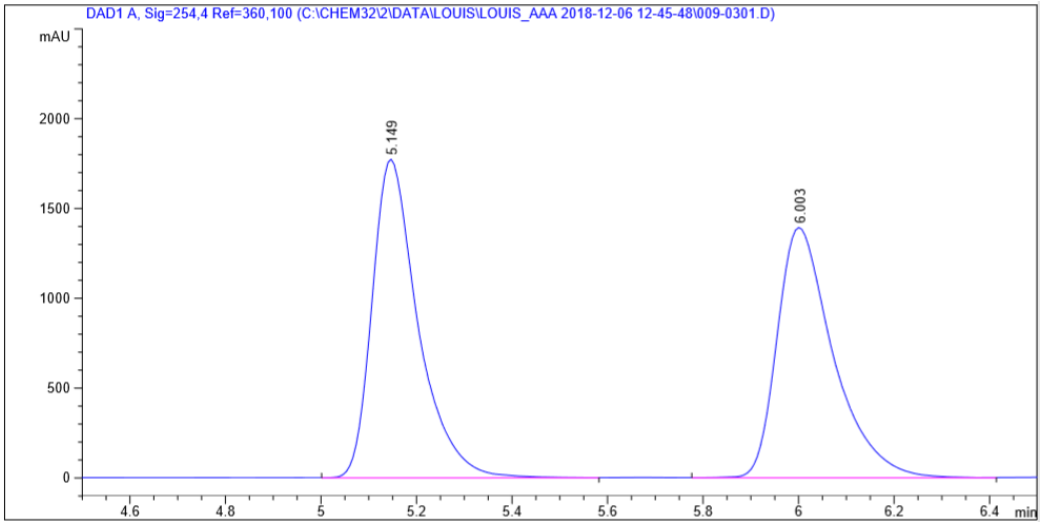
FTIR (neat): 3314, 2918, 1576, 1498, 1422, 1377, 1256, 1214, 1081, 955, 918, 814, 684 cm^{-1}.

$[\alpha]_D^{28}$ = –1.8 (*c* 1.0, $CHCl_3$).

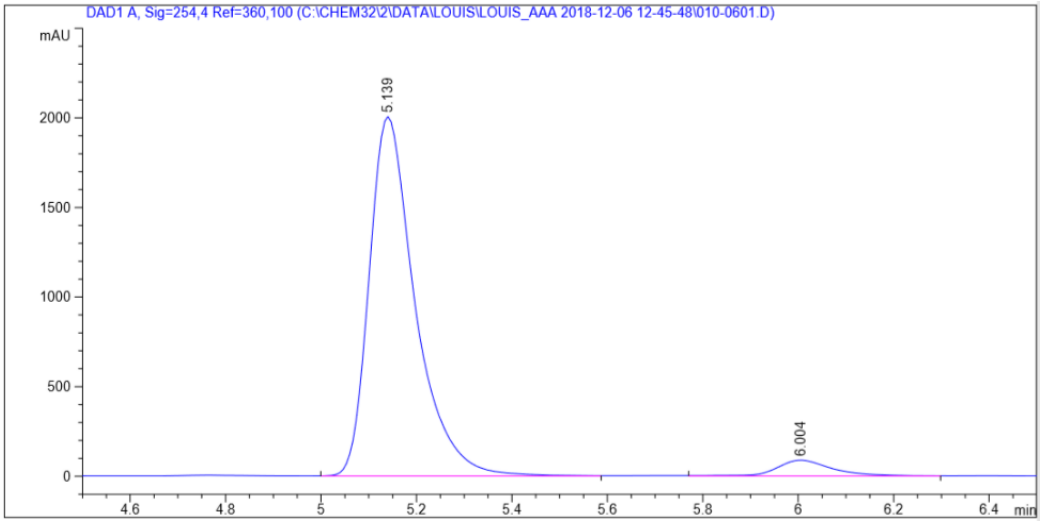
HPLC (Chiralcel OD-3 column, hexanes:*i*-PrOH = 90:10, 1.00 mL/min, 254 nm), *ee* = 90%.


HN
H
N
O
Me
Br
4.7b
^{1}H (400 MHz, $CDCl_3$)
f1 (ppm)


HN
H
N
O
Me
Br
4.7b
^{13}C (100 MHz, $CDCl_3$)
f1 (ppm)

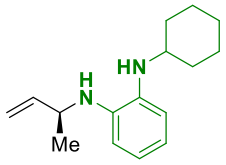


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.149	VV	0.0999	1.18412e4	1774.31335	51.0129
2	6.003	VV	0.1211	1.13710e4	1394.24512	48.9871



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.139	BV	0.1000	1.34241e4	2006.97974	94.8630
2	6.004	VV	0.1213	726.94116	89.03390	5.1370

(*S*)-N1-(but-3-en-2-yl)-N2-cyclohexylbenzene-1,2-diamine (4.7c)



4.7c

The allylic acetate (50.2 mg, 0.44 mmol, 100 mol%) and the amine (167.4 mg, 0.88 mmol, 200 mol%) were subject to standard reaction conditions (60 °C, 24 hr). The title compound was obtained in 86% yield (92.5 mg, 0.38 mmol) as a light yellow oil after purification by flash column chromatography (12g SiO_2, Isopropyl Acetate / Heptane = 0% - 5% over 20 min).

TLC (SiO_2) R_f = 0.46 (hexanes: ethyl acetate = 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.80 – 6.65 (m, 4H), 6.01 – 5.76 (m, 1H), 5.21 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.08 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.93 (p, *J* = 6.5 Hz, 1H), 3.38 – 3.11 (m, 3H), 2.12 – 1.99 (m, 2H), 1.84 – 1.72 (m, 2H), 1.66 (dt, *J* = 13.1, 3.9 Hz, 1H), 1.39 (dd, *J* = 14.7, 11.5 Hz, 2H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.31 – 1.14 (m, 3H).

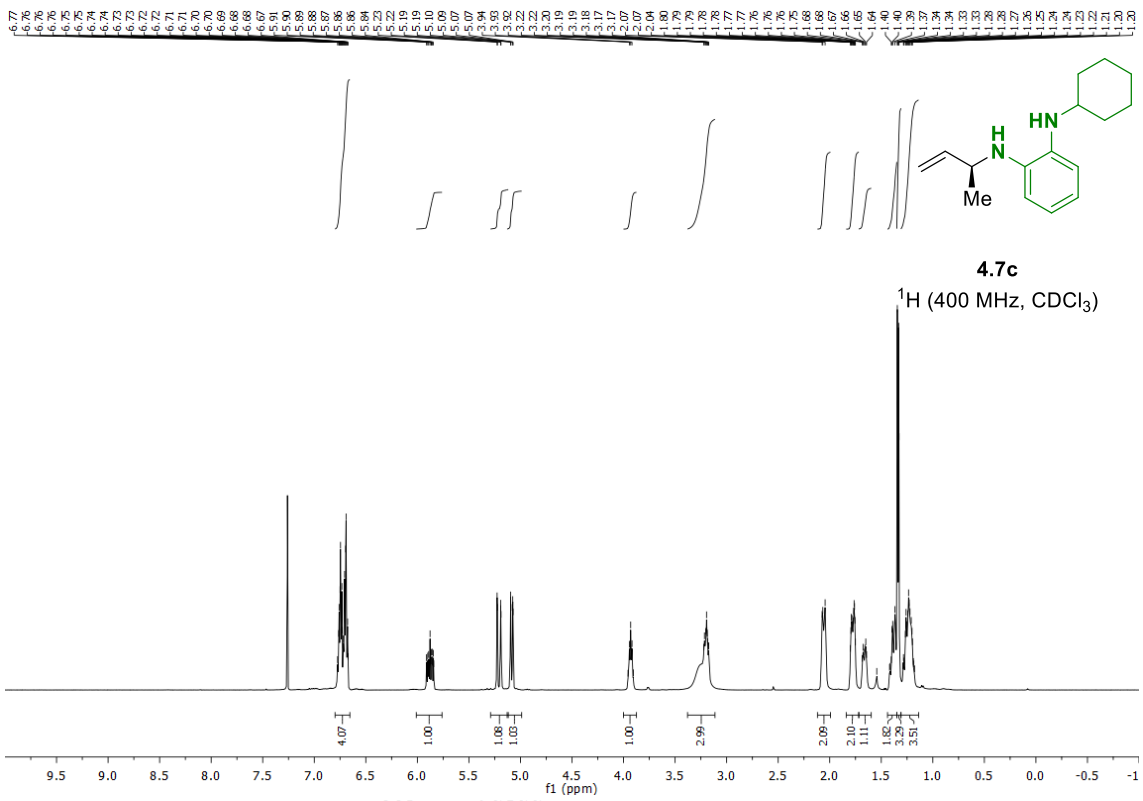
^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 136.7, 136.5, 119.2, 118.8, 114.0, 113.9, 113.4, 52.1, 51.5, 33.7 (d), 26.10, 25.0 (d), 21.87.

HRMS (ESI): Calculated for $C_{16}H_{24}N_2$ [M+H$^+$] = 245.2012, Found 245.2016.

FTIR (neat): 3330, 2926, 1598, 1508, 1448, 1304, 1252, 1148, 916, 733 cm^{-1}.

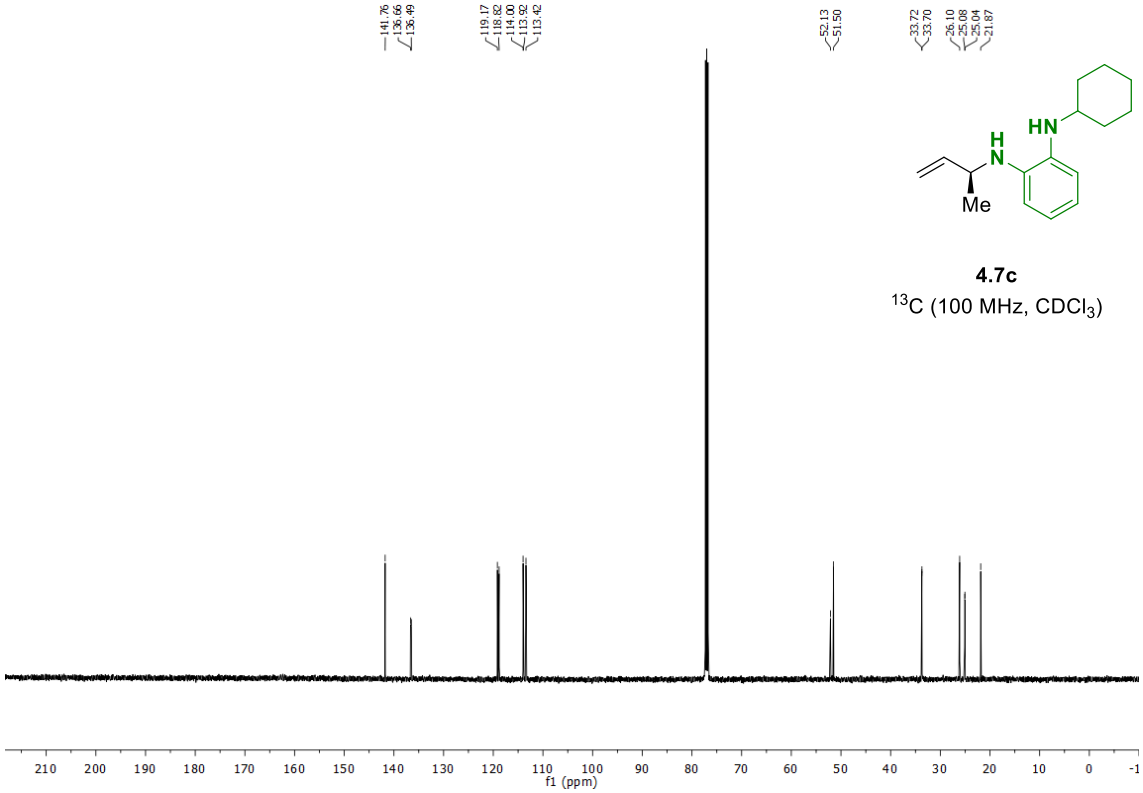
$[\alpha]_D^{28}$= +30.0 (*c* 0.1, $CHCl_3$).

HPLC (Chiralcel AD-H column, heptanes:*i*-PrOH = 98:2, 1.00 mL/min, 254 nm), *ee* = 92%.



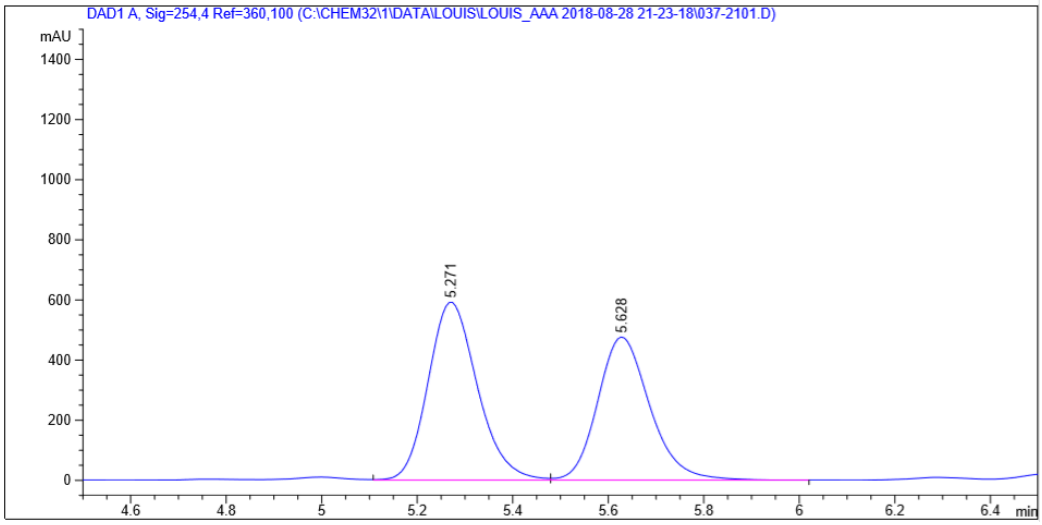
4.7c

^{1}H (400 MHz, $CDCl_3$)

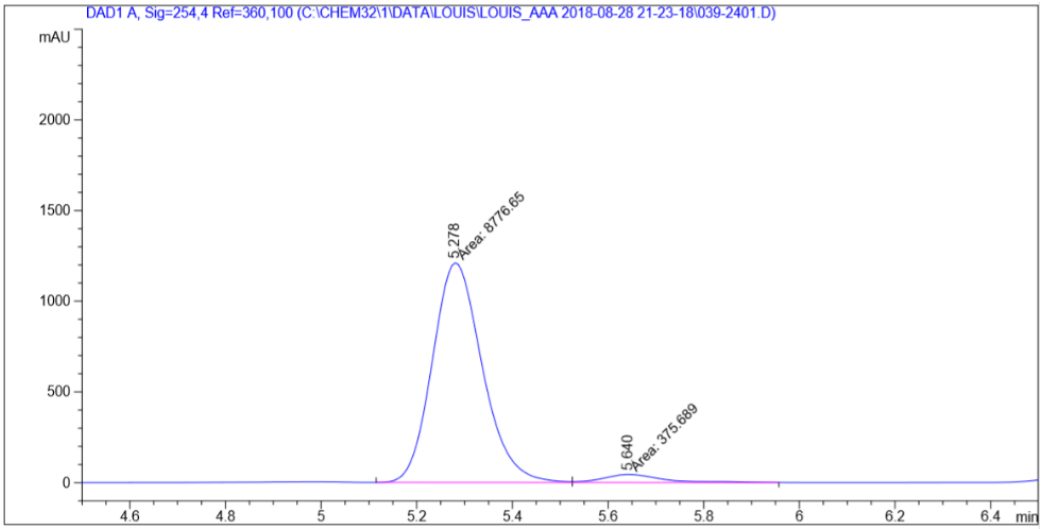


4.7c

^{13}C (100 MHz, $CDCl_3$)



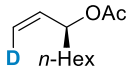
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.271	VV	0.1116	4247.09521	593.03601	54.0182
2	5.628	VB	0.1165	3615.25073	476.42450	45.9818



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.278	MF	0.1207	8776.64844	1211.57275	95.8952
2	5.640	FM	0.1409	375.68869	44.43553	4.1048

4.5.3.3 Procedures and Spectral Data for Deuterium Labelling Experiments

(*S*,*Z*)-oct-1-en-3-yl-1-d acetate (4.1h)



4.1h

1h synthesized from commercially available (*S*)-(-)-1-Octyn-3-ol, >98% ee.

To a round-bottomed flask charged with potassium carbonate (380.1 mg, 2.8 mmol, 110 mol%) was added deuterium oxide (6.8 mL, 0.37 M, 99.9 atom % D), followed by (*S*)-(-)-1-Octyn-3-ol (315 mg, 2.5 mmol, 100 mol%). The mixture was stirred at room temperature overnight. After anhydrous CH_2Cl_2 (10 mL) were added to the reaction mixture, the mixture was transferred to a separatory funnel. The organic layer was extracted with CH_2Cl_2 (5 mL × 2) and the combined organic layers were washed with H_2O (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to the next step without further purification.

To a round-bottomed flask charged with the crude substrate under an argon atmosphere was added anhydrous CH_2Cl_2 (10 mL, 0.25 M with respect to propargylic alcohol). The reaction vessel was placed in an ice batch. After 5 minutes DIBAL (3 mL, 3.0 mmol, 1 M in hexanes) was added slowly and the solution was stirred at room temperature for 30 minutes. After the reaction vessel was placed in an ice batch, Schwartz's reagent (773.6 mg, 3.0 mmol, 120 mol%) was added to the reaction mixture. The mixture was stirred at room temperature for 2 hours, at which point saturated aqueous sodium bicarbonate (5 mL) were added and the reaction was stirred vigorously. After 2 hours, the reaction mixture was filtered (celite) with the aid of CH_2Cl_2 (10 mL) and the filtrate was transferred to a separatory funnel. The organic layer was extracted with CH_2Cl_2 (10 mL × 2) and the

combined organic layers were washed with H_2O (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to the next step without further purification.

To a round-bottomed flask charged with the crude substrate and 4-dimethylaminopyridine (15.2 mg, 0.13 mmol, 5 mol%) under an argon atmosphere was added CH_2Cl_2 (12.5 mL, 0.25 M with respect to propargylic alcohol), followed by acetic anhydride (0.28 mL, 3.0 mmol, 120 mol%) and triethylamine (0.41 mL, 3.0 mmol, 120 mol%). After 1 hour, saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was transferred to a separatory funnel. The organic layer was extracted with CH_2Cl_2 (10 mL × 2) and the combined organic layers were washed with 1 N HCl (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oily residue was subjected to flash column chromatography (SiO_2, hexanes: ethyl acetate = 30:1) to furnish the title compound as a light yellow oil (240 mg, 1.40 mmol) in 56% yield over 3 steps.

TLC (SiO_2) R_f = 0.72 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (ddt, J = 10.4, 6.3, 2.6 Hz, 1H), 5.25 – 5.19 (m, 1H), 5.14 (dd, J = 10.5, 1.1 Hz, 1H), 2.06 (s, 3H), 1.66 – 1.52 (m, 2H), 1.34 – 1.25 (m, 6H), 0.91 – 0.84 (m, 3H).

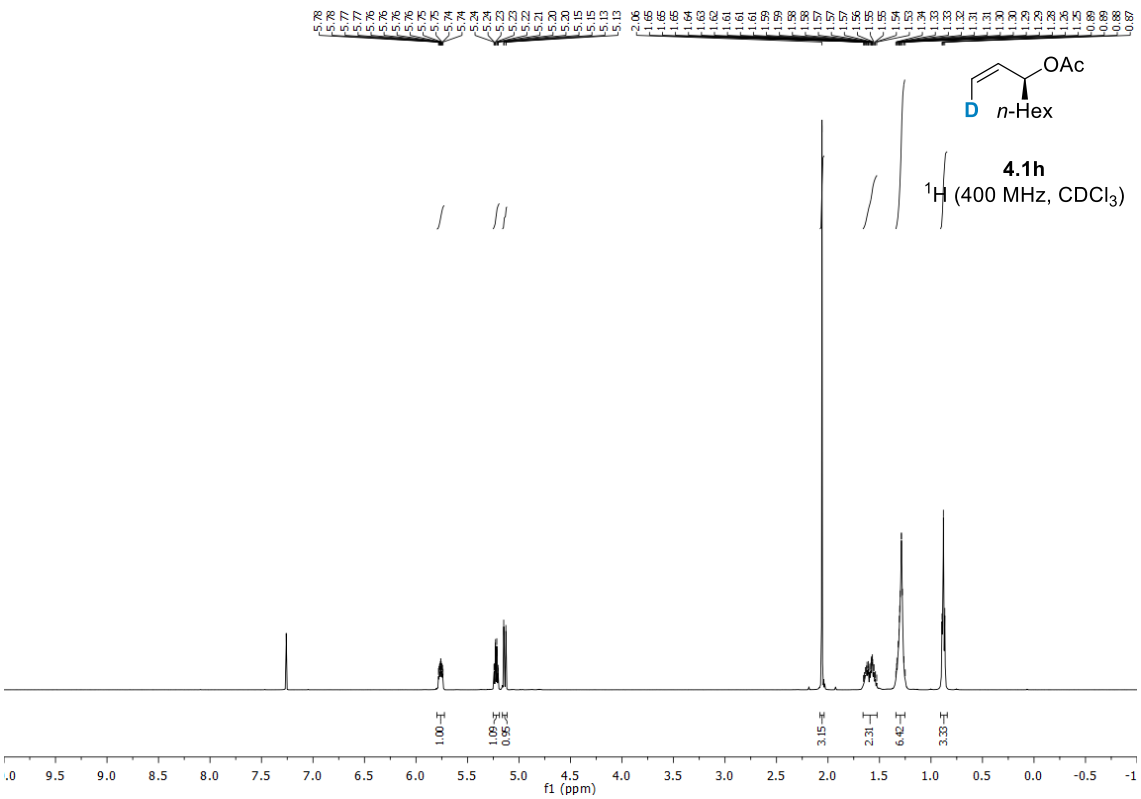
^{2}H NMR (92 MHz, $CHCl_3$): δ = 5.28 (s, 1D).

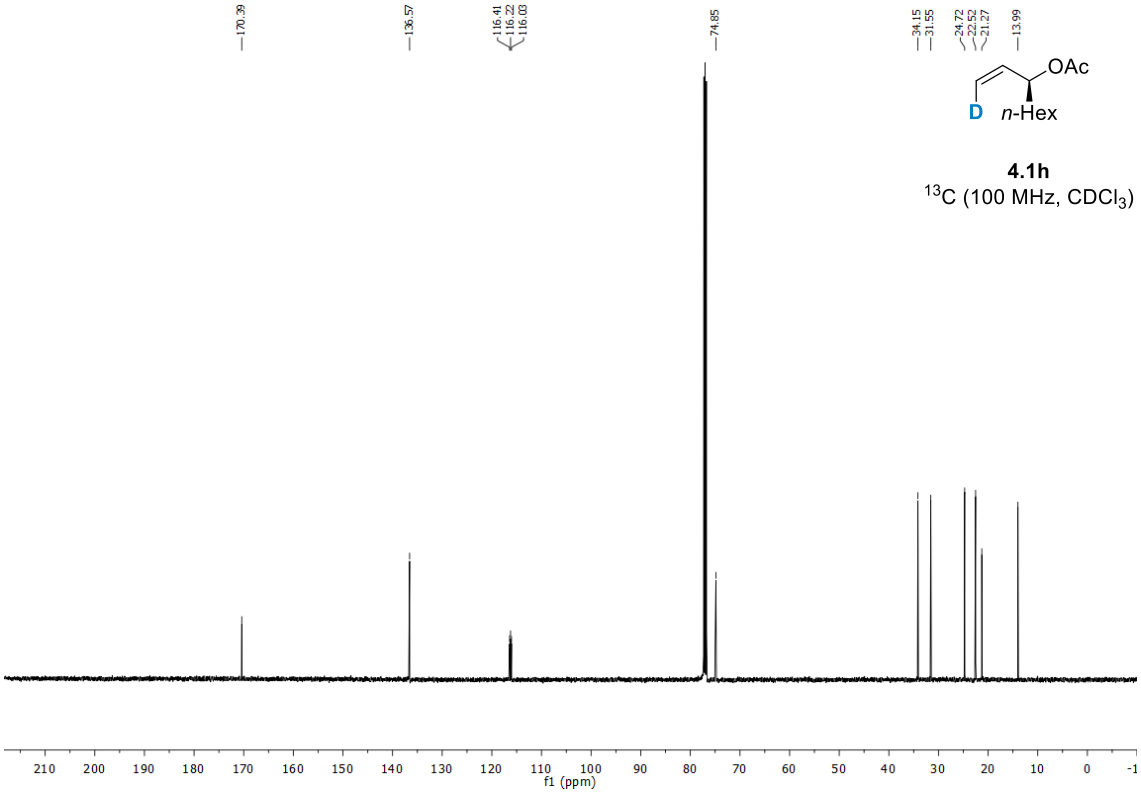
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 136.6, 116.2 (t), 74.9, 34.2, 31.6, 24.7, 22.5, 21.3, 14.0.

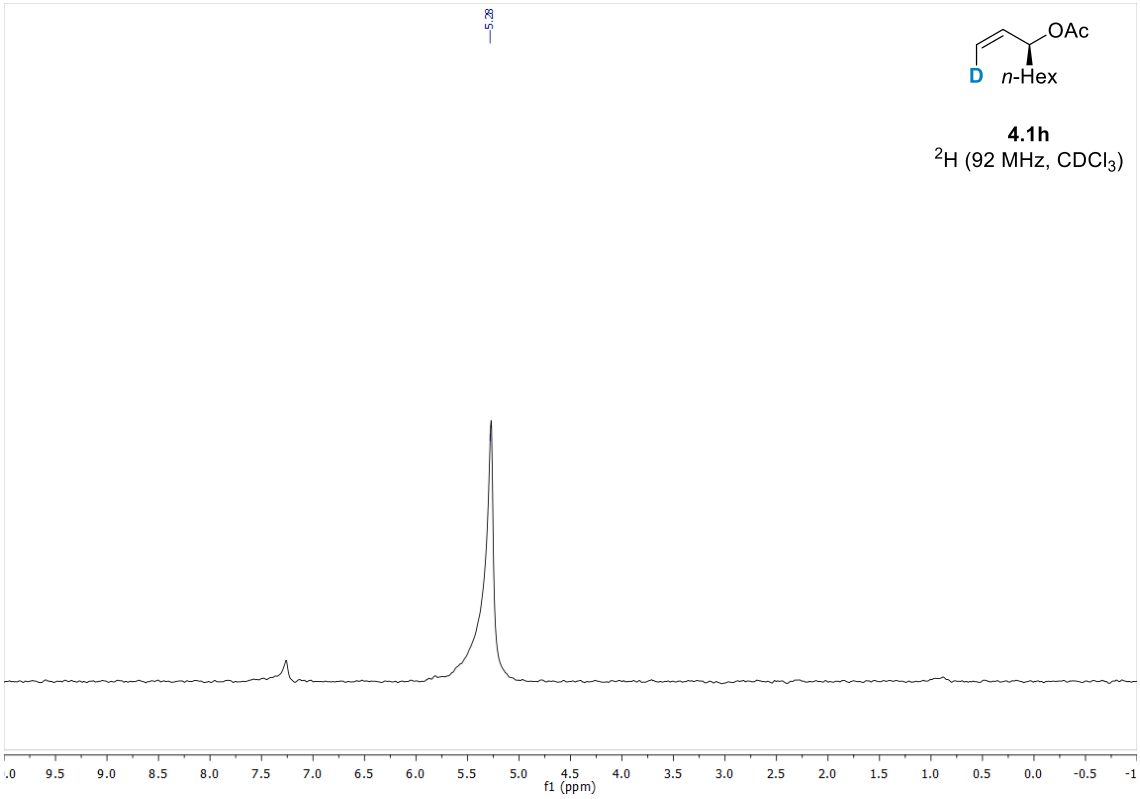
LRMS (CI): Calculated for $C_8H_{14}D$ $[M–OAc]^+$ = 112, Found 112.

FTIR (neat): 2932, 1731, 1372, 1247, 1021, 756, 667 cm^{-1}.

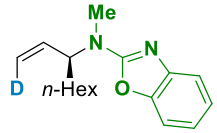
$[\alpha]_D^{28}$= – 74.5(*c* 1.0, $CHCl_3$).


OAc
D
n-Hex
4.1h
1H (400 MHz, CDCl3)
f1 (ppm)


OAc
D
n-Hex
4.1h
13C (100 MHz, CDCl3)
f1 (ppm)


5.28
OAc
D
n-Hex
4.1h
2H (92 MHz, CDCl3)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

(*S*,*Z*)-N-methyl-N-(oct-1-en-3-yl-1-d)benzo[d]oxazol-2-amine (4.8a)



4.8a

An pressure tube equipped with a magnetic stir bar was charged with amine **4.3m** (59.3 mg, 0.4 mmol, 200 mol%), cesium carbonate (130.3 mg, 0.4 mmol, 200 mol%) and (*S*)-Ir-**II** (11.1 mg, 0.01 mmol, 5 mol%). The tube was purged with argon for 5 minutes. DME (0.2 mL, 1.0 M) was added followed by the deuterated allylic acetate **4.1h** (34.3 mg, 0.2 mmol, 100 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at 70 °C for 24 hours. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography (SiO_2, hexanes: ethyl acetate = 25:1–15:1). The title compound was obtained in 89% yield (46.2 mg, 0.18 mmol) as a colorless oil.

TLC (SiO_2) R_f = 0.55 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (dd, J = 7.8, 1.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.15 (td, J = 7.7, 1.1 Hz, 1H), 6.99 (td, J = 7.7, 1.2 Hz, 1H), 5.85 (ddd, J = 10.5, 5.1, 2.4 Hz, 1H), 5.20 (dd, J = 10.6, 1.6 Hz, 1H), 4.86 – 4.77 (m, 1H), 3.02 (s, 3H), 1.74 – 1.66 (m, 2H), 1.36 – 1.27 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H).

^{2}H NMR (92 MHz, $CHCl_3$): δ = 5.28 (s, 1D).

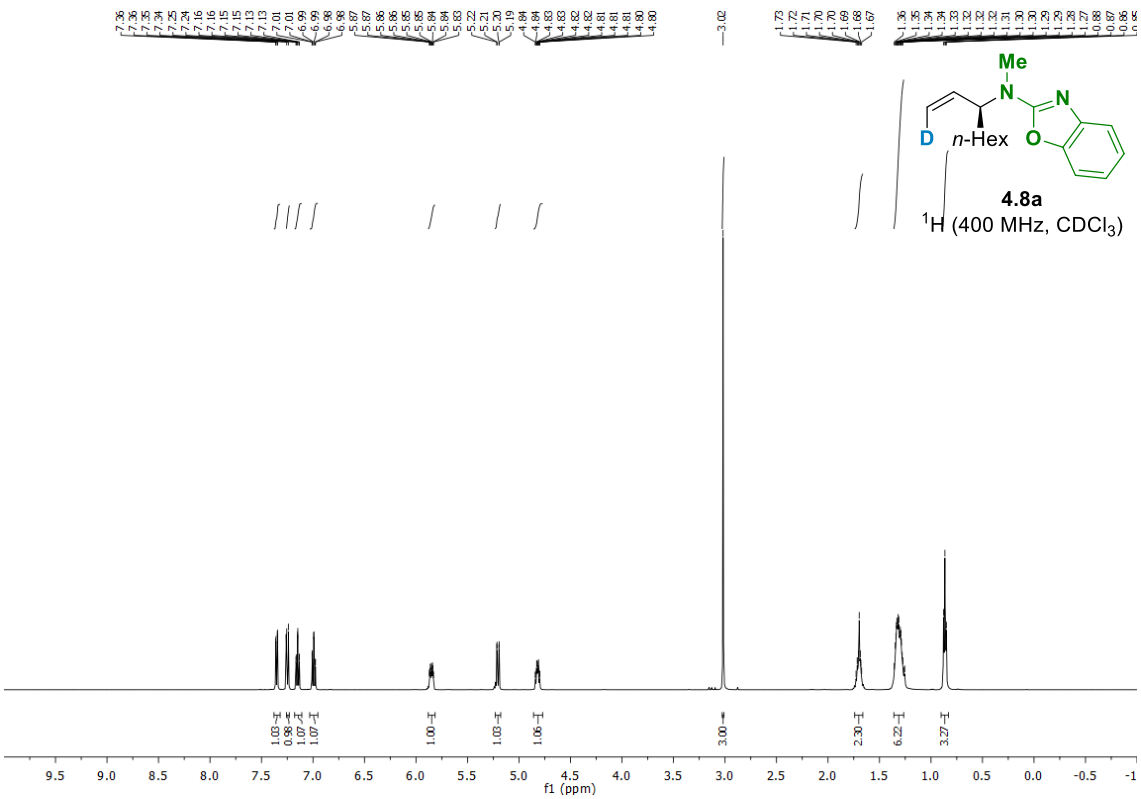
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 148.8, 143.5, 136.1, 123.8, 120.1, 116.4 (t), 116.0, 108.6, 58.9, 31.6, 30.9, 29.7, 25.8, 22.5, 14.0.

HRMS (ESI): Calculated for $C_{16}H_{21}DN_2O$ $[M+H^+]$ = 260.1868, Found 260.1870.

FTIR (neat): 2930, 1636, 1577, 1460, 1246, 1216, 748 cm^{-1}.

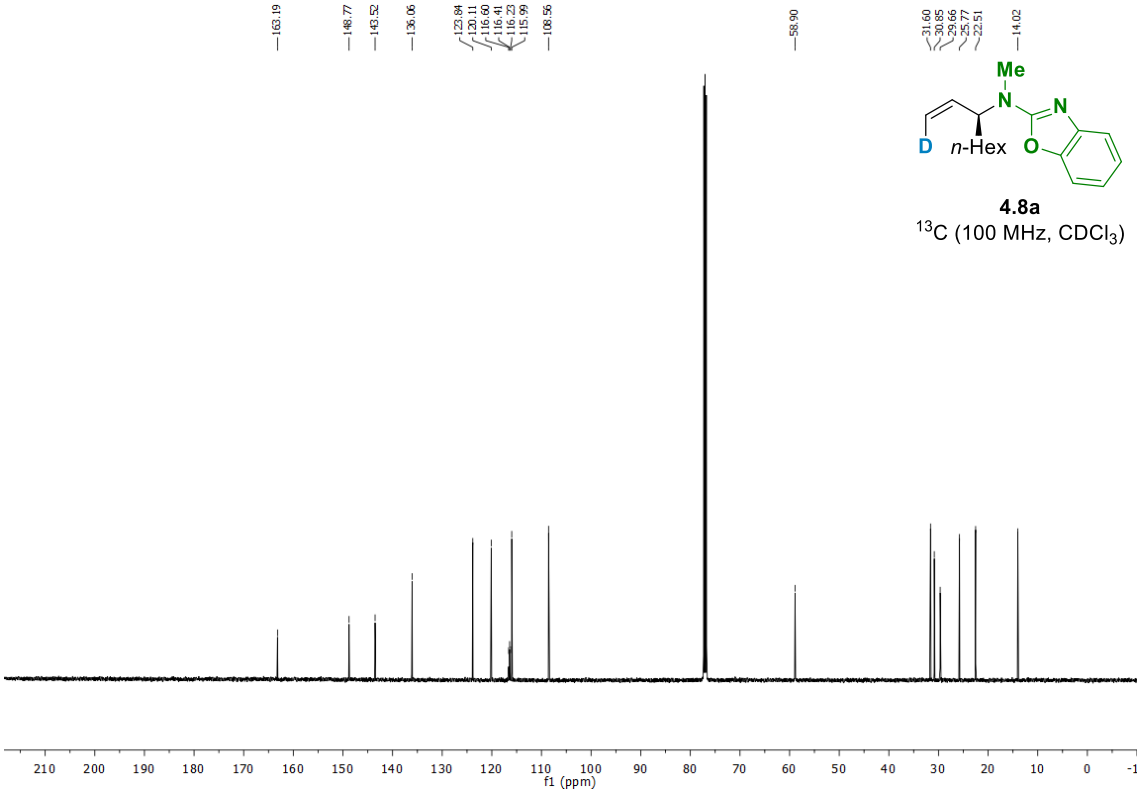
$[\alpha]_D^{28}$= –71.3 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, heptanes:*i*-PrOH = 98:2, 1.00 mL/min, 254 nm), *ee* = 87%**.**



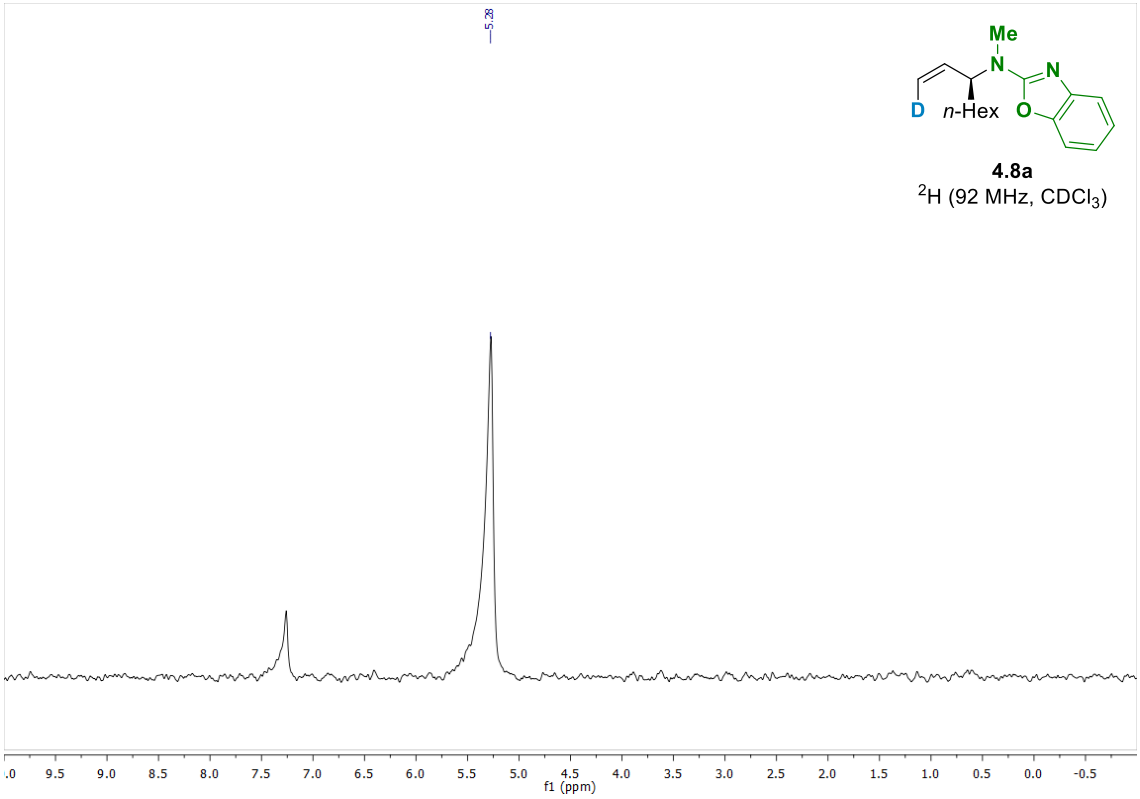
4.8a

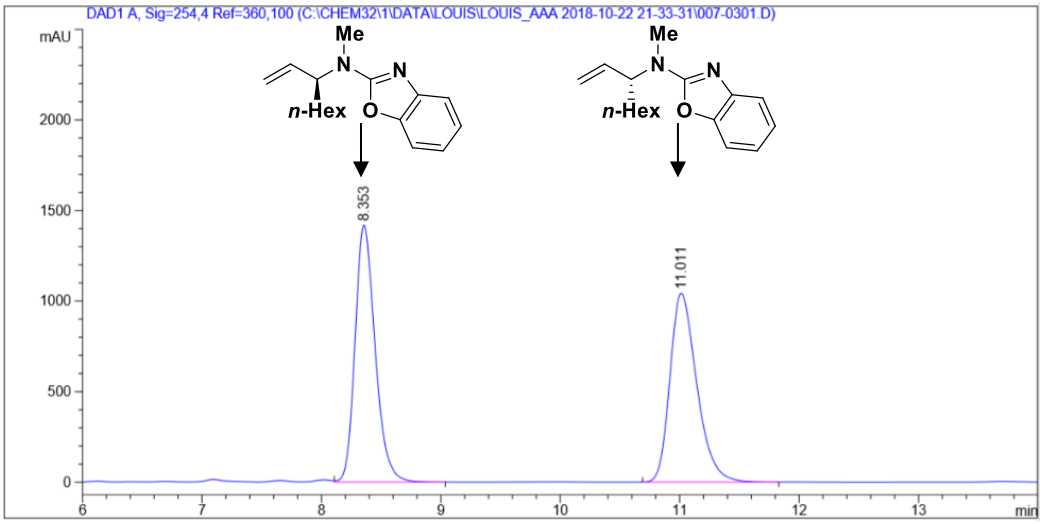
^{1}H (400 MHz, $CDCl_3$)



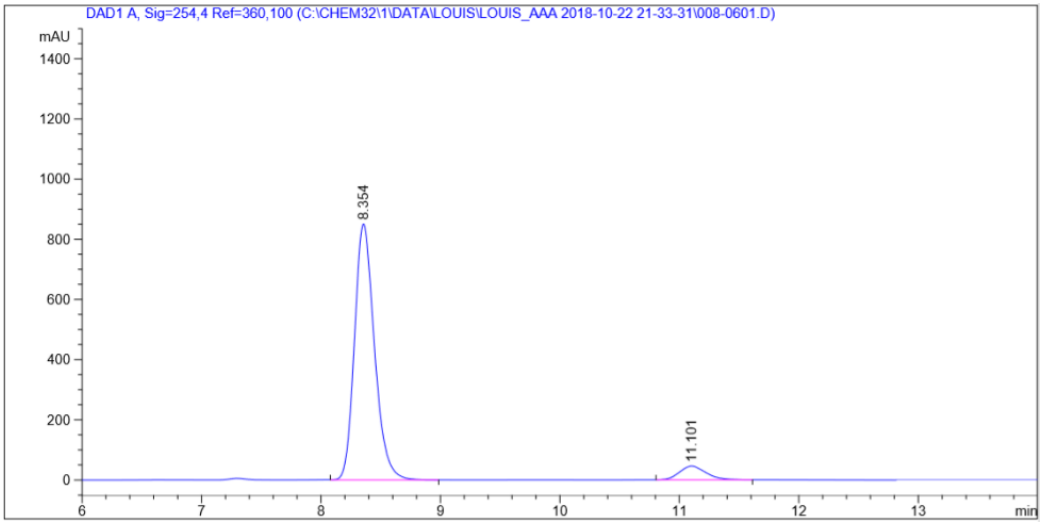
4.8a

^{13}C (100 MHz, $CDCl_3$)


5.38
Me
N
N
D
n-Hex
O
4.8a
2H (92 MHz, CDCl3)
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

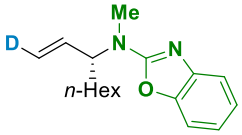


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.353	VB	0.1803	1.65706e4	1418.74658	50.4411
2	11.011	BB	0.2382	1.62808e4	1042.75146	49.5589



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.354	VB	0.1794	9878.64551	851.14398	93.3375
2	11.101	BB	0.2386	705.14496	45.54940	6.6625

(*R*,*E*)-N-methyl-N-(oct-1-en-3-yl-1-d)benzo[d]oxazol-2-amine (4.8b)



4.8b

An pressure tube equipped with a magnetic stir bar was charged with amine **4.3m** (59.3 mg, 0.4 mmol, 200 mol%), cesium carbonate (130.3 mg, 0.4 mmol, 200 mol%) and (*R*)-Ir-**II** (11.1 mg, 0.01 mmol, 5 mol%). The tube was purged with argon for 5 minutes. DME (0.2 mL, 1.0 M) was added followed by the deuterated allylic acetate **4.1h** (34.3 mg, 0.2 mmol, 100 mol%). The tube was sealed with a PTFE lined cap and was placed in an oil bath at 70 ^{o}C for 24 hours. After reaching ambient temperature, the crude reaction mixture was directly subjected to flash column chromatography (SiO_2, hexanes: ethyl acetate = 25:1–15:1). The title compound was obtained in 85% yield (44.1 mg, 0.17 mmol) as a colorless oil.

TLC (SiO_2) R_f = 0.55 (hexanes: ethyl acetate = 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (dd, J = 7.8, 1.1 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.15 (td, J = 7.7, 1.1 Hz, 1H), 6.99 (td, J = 7.8, 1.2 Hz, 1H), 5.86 (dd, J = 17.3, 5.3 Hz, 1H), 5.21 (dd, J = 17.4, 1.7 Hz, 1H), 4.82 (dddd, J = 8.6, 6.8, 5.3, 1.7 Hz, 1H), 3.02 (s, 3H), 1.76 – 1.63 (m, 2H), 1.41 – 1.21 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H).

^{2}H NMR (92 MHz, $CHCl_3$): δ = 5.28 (s, 1D).

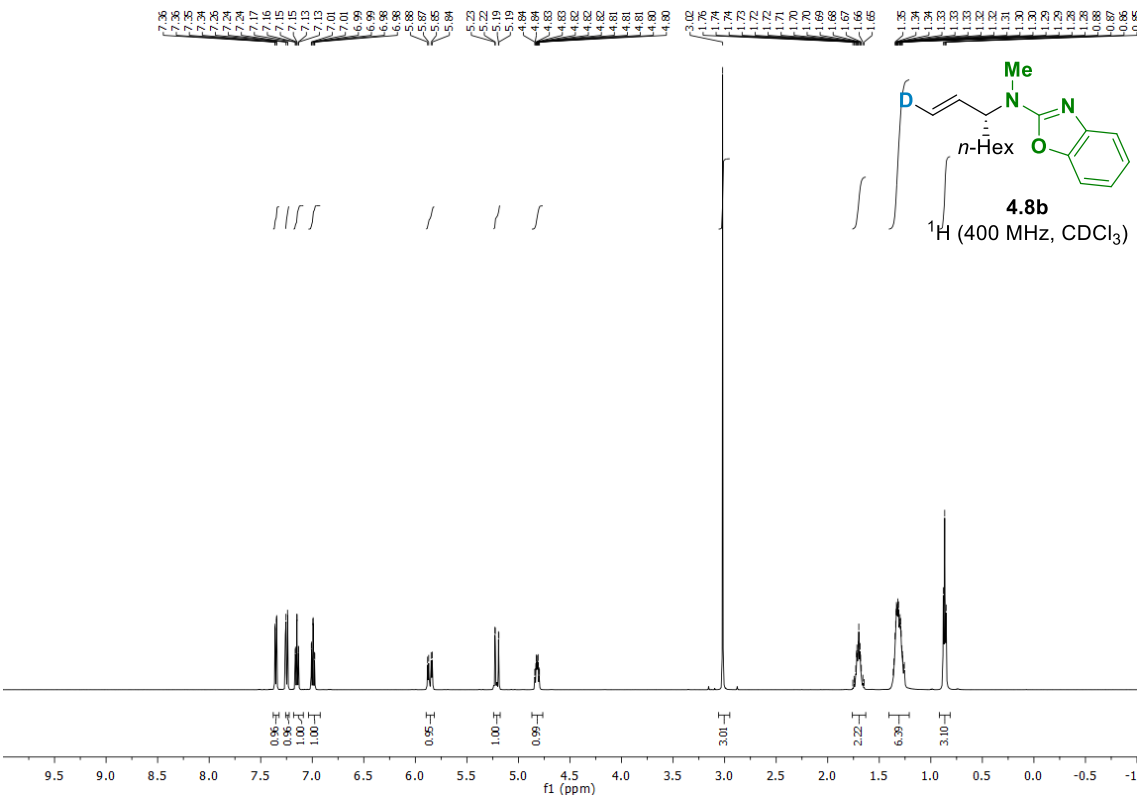
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 148.8, 143.5, 136.2, 136.0, 123.8, 120.1, 116.6, 116.4, 116.2, 116.0, 108.6, 58.9, 31.6, 30.9, 29.7, 25.8, 22.5, 14.0.

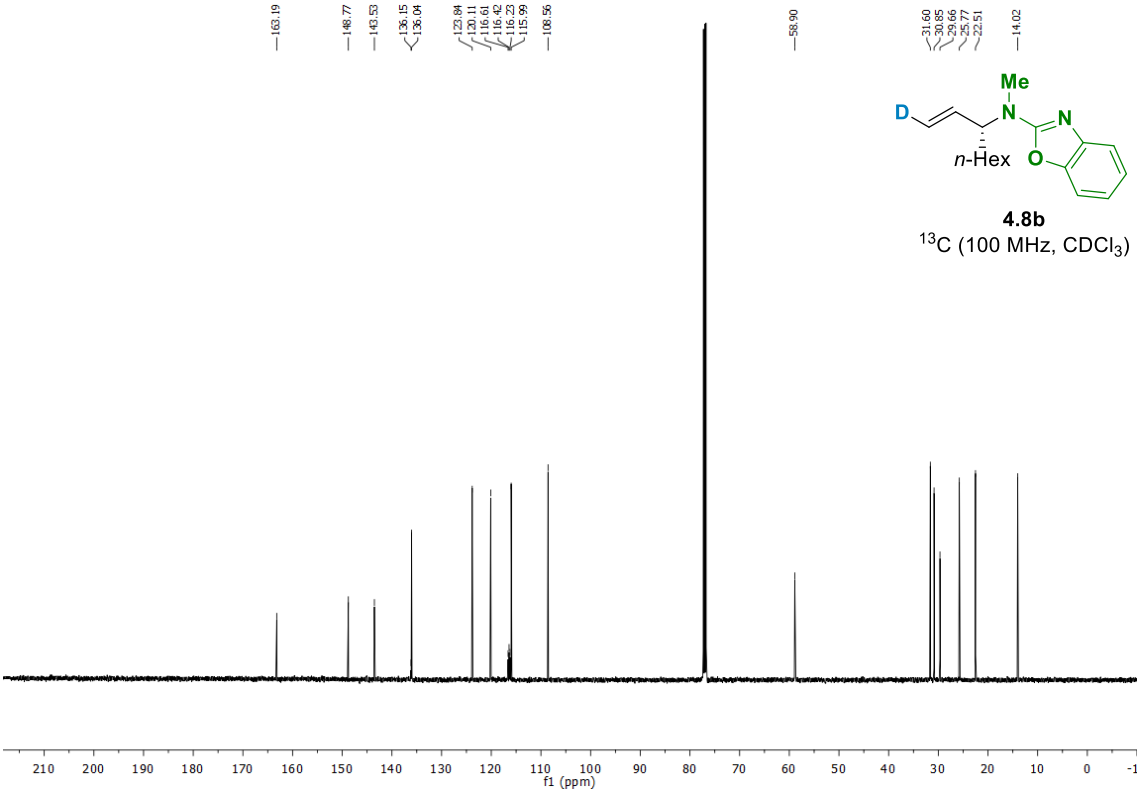
HRMS (ESI): Calculated for $C_{16}H_{21}DN_2O$ [M+H$^+$] = 260.1868, Found 260.1872.

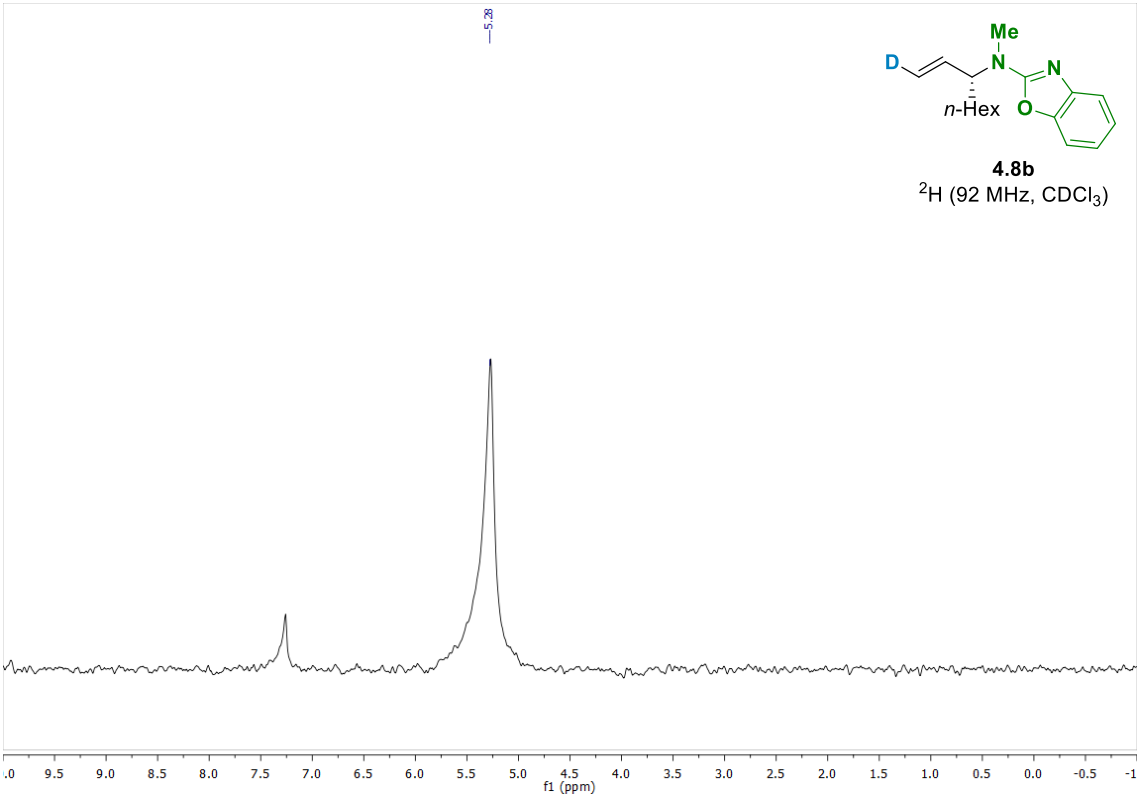
FTIR (neat): 2930, 1636, 1577, 1460, 1246, 1216, 753 cm^{-1}.

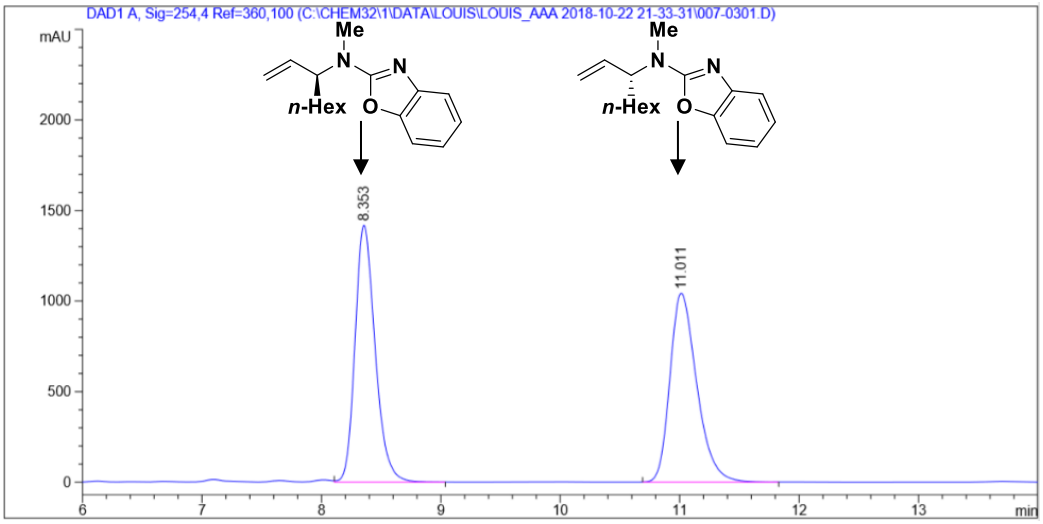
$\mathbf{[\alpha]_D^{28}}$**=** +70.8 (*c* 1.0, $CHCl_3$).

HPLC (Chiralcel AD-H column, heptanes:*i*-PrOH = 98:2, 1.00 mL/min, 254 nm), *ee* = 96%.

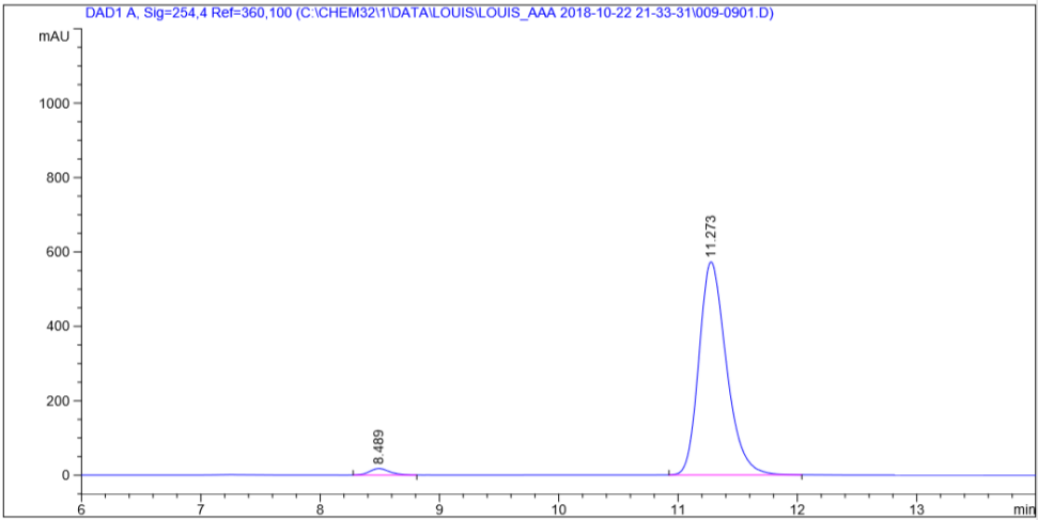

Me
N
D
N
O
n-Hex
4.8b
1H (400 MHz, CDCl3)
f1 (ppm)


Me
N
D
N
O
n-Hex
4.8b
13C (100 MHz, CDCl3)
f1 (ppm)


5.28
Me
D
N
N
n-Hex
O
4.8b
2H (92 MHz, CDCl3)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.353	VB	0.1803	1.65706e4	1418.74658	50.4411
2	11.011	BB	0.2382	1.62808e4	1042.75146	49.5589

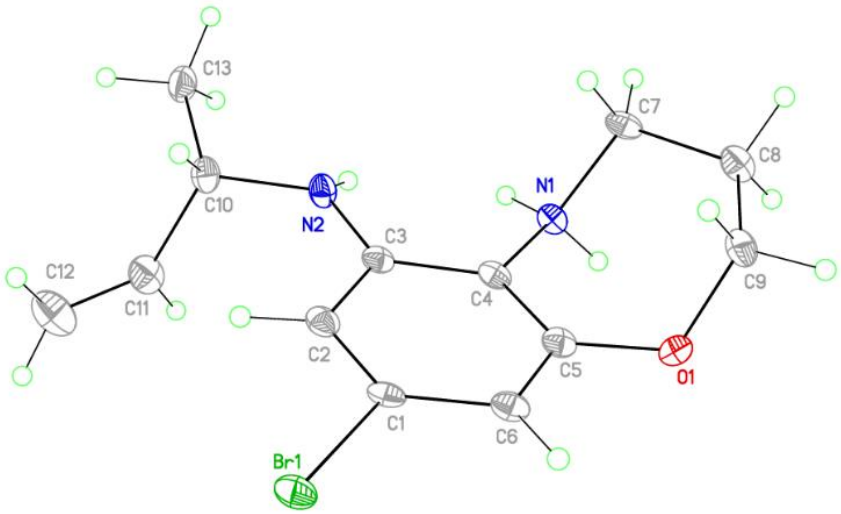


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.489	BB	0.1769	204.68243	17.69532	2.1833
2	11.273	BB	0.2468	9170.32715	572.78448	97.8167

4.5.3.4 Single Crystal Diffraction Data for 4.7b

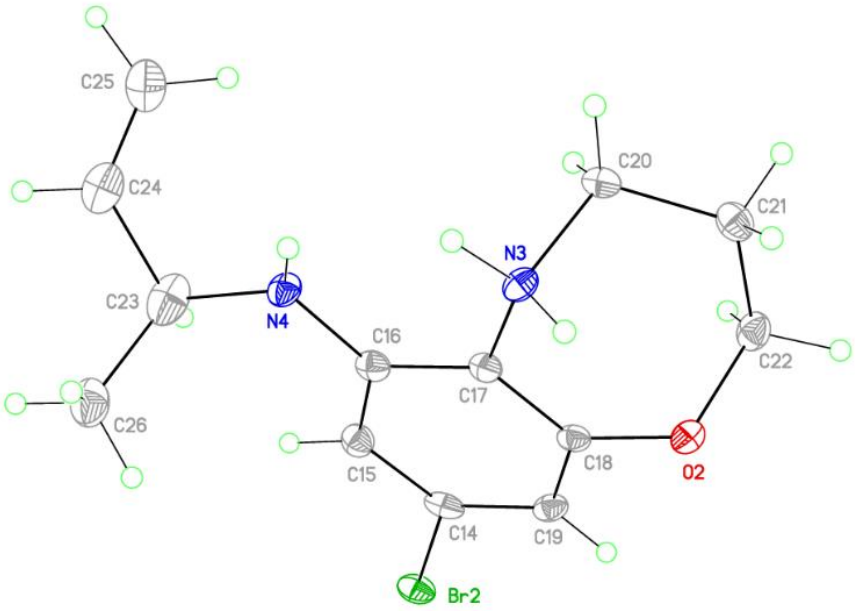
Empirical formula	C13 H18 Br Cl N2 O	
Formula weight	333.65	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.1967(3) Å	α= 90°.
	b = 19.2597(4) Å	β= 105.491(5)°.
	c = 10.4450(4) Å	γ = 90°.
Volume	1395.15(9) $Å^3$	
Z	4	
Density (calculated)	1.588 Mg/m^3	
Absorption coefficient	5.697 mm^{-1}	
F(000)	680	
Crystal size	0.160 x 0.070 x 0.030 mm^3	
Theta range for data collection	4.393 to 75.594°.	
Index ranges	-8<=h<=8, -23<=k<=23, -12<=l<=12	
Reflections collected	21291	
Independent reflections	5628 [R(int) = 0.0497]	
Completeness to theta = 67.684°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5628 / 2 / 351	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0362, wR2 = 0.0947	
R indices (all data)	R1 = 0.0369, wR2 = 0.0955	
Absolute structure parameter	-0.009(15)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.701 and -0.579 $e.Å^{-3}$	

Figure 4.2 Crystal Structure of **4.7b** Cation 1



View of cation 1 in **4.7b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

Figure 4.3 Crystal Structure of **4.7b** Cation 2



View of cation 2 in **4.7b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

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Chapter 2

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